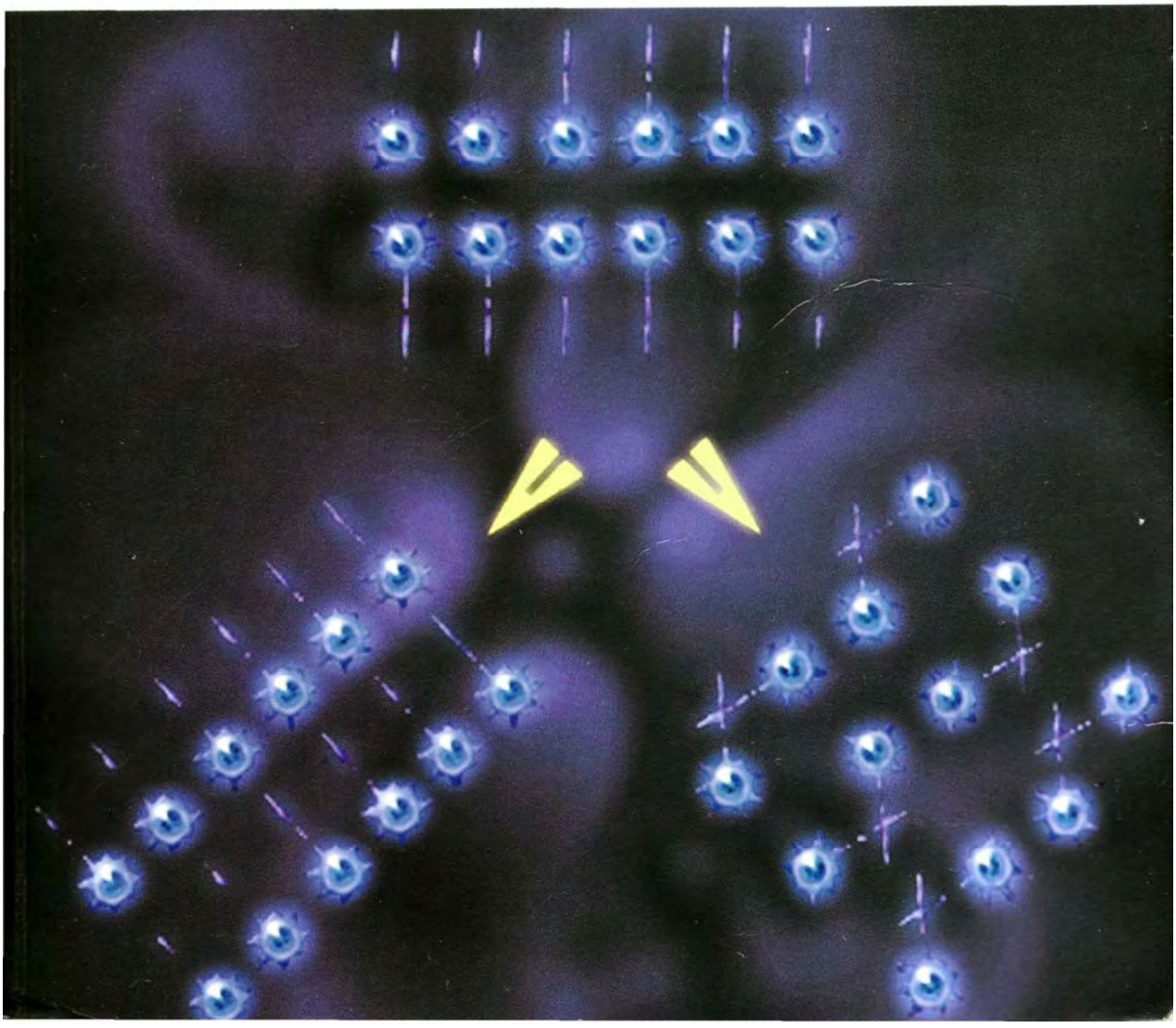
Stephen M. Stahl

Essential Psychopharmacology

Neuroscientific Basis and Practical Applications

Second Edition



Essential Psychopharmacology

Stahl's *Essential Psychopharmacology* has established itself as the preeminent source of education and information in its field. This much expanded second edition enlists advances in neurobiology and recent clinical developments to explain with renewed clarity the concepts underlying drug treatment of psychiatric disorders. New neurotransmitter systems, new theories of schizophrenia, clinical advances in antipsychotic and antidepressant therapy, new coverage of attention deficit disorder, sleep disorders, and drug abuse, and a new chapter on sex-specific and sexual function-related psychopharmacology—these are all features of this edition.

The fully revised text is complemented by many new illustrations, which are instructive and entertaining as before and enhanced to reflect new knowledge and topics covered for the first time. The illustrations and their captions may be used independently of the main text for a rapid introduction to the field or for review. CME self-assessment tests are also included.

Even more, this will be the essential text for students, scientists, psychiatrists, and other mental health professionals, enabling them to master the complexities of psychopharmacology and plan sound treatment approaches based on current knowledge.

Stephen M. Stahl is Adjunct Professor of Psychiatry at the University of California, San Diego. He received his undergraduate and medical degrees from Northwestern University in Chicago and his Ph.D. degree in pharmacology and physiology from the University of Chicago and has trained in three specialties, internal medicine, neurology, and psychiatry. As a faculty member at Stanford University, the University of California at Los Angeles, the Institute of Psychiatry in London, and currently at the University of California at San Diego, Dr. Stahl has conducted numerous research projects awarded by the National Institute of Mental Health, the Veterans Administration, and the pharmaceutical industry. The author of more than 200 articles and chapters, Dr. Stahl is an internationally recognized clinician, researcher, and teacher. Lectures and courses based on *Essential Psychopharmacology* have taken him to dozens of countries to speak to tens of thousands of physicians, mental health professionals, and students at all levels.

ESSENTIAL PSYCHOPHARMACOLOGY

Neuroscientific Basis and Practical Applications
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With illustrations by Nancy Muntner

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Rewiews of *Essential Psychopharmacology, First Edition*

"Essential reading . . . I would thoroughly recommend this book to anyone who works with psychotropic drugs—or who has the task of teaching others about them!"
American Journal of Psychiatry

"Firmly grounded in contemporary neuroscience . . . an excellent and comprehensive account of the pharmacology of drugs currently used to treat psychiatric disorders."
Psychological Medicine

"This masterful production will benefit a broad spectrum of readers, from students to knowledgeable and experienced psychopharmacologists."
Psychiatric Times

"Finally, an elegant and beautiful psychopharmacology text written by a basic scientist who is also a clinician."
Journal of Clinical Psychiatry

In memory of Daniel X. Freedman, mentor, colleague, and scientific father. To

Cindy, my wife, best friend, and tireless supporter.

To Jennifer and Victoria, my daughters, for their patience and understanding of the demands of authorship.

PREFACE TO THE SECOND EDITION

Much has changed in psychopharmacology since the publication of the first edition of *Essential Psychopharmacology* four years ago. This second edition attempts to reflect the advances in neuroscience, in the understanding of psychiatric disorders, and in the dozens of new medications for psychiatric disorders that have dramatically advanced the field of psychopharmacology in this brief period of time. Thus, two chapters have been added, 11 of the 12 earlier chapters have been extensively revised, and the length of the written text has been increased by about 50%. What has not changed is the didactic style of the first edition, which continues in this edition and is largely based on updated lectures, slides, and articles of the author. Thus, new materials are presented, with an emphasis on color pictures, which have more than doubled in this edition to over 500 in total.

Also newly included in this edition are materials at the end of each chapter for readers interested in using the text materials to receive continuing medical education credits. Since the lessons in these chapters are used widely by the author for lecturing to medical practitioners, they have been accredited by the University of California, San Diego as enduring materials for up to 54 category I continuing medical education credit hours according to the guidelines of the Accreditation Council of Continuing Medical Education (ACCME) of the American Medical Association. Tests are included at the end of each chapter, and instructions for submitting them and the required fees are all explained at the end of the textbook for those readers who are interested.

In general, this text attempts to present the fundamentals of psychopharmacology in simplified and readily readable form. Thus, this material should prepare the reader to consult more sophisticated textbooks as well as the professional literature. The organization of the information here also applies principles of programmed learning for the reader, namely repetition and interaction, which have been shown to enhance retention.

Therefore, it is suggested that novices first approach this text by going through it from beginning to end, reviewing only the color graphics and the legends for these graphics. Virtually everything covered in the text is also covered in the graphics and icons. Once having gone through all the color graphics in these chapters, it is recommended that the reader then go back to the beginning of the book and read the entire text, reviewing the graphics at the same time. Finally, after the text has been read, the entire book can be rapidly reviewed merely by referring to the various color graphics.

This approach to using the materials will create a certain amount of programmed learning by incorporating the elements of repetition as well as interaction with visual learning through graphics. Hopefully, the visual concepts learned via graphics will reinforce abstract concepts learned from the written text, especially for those of you who are primarily "visual learners" (i.e., those who retain information better from visualizing concepts than from reading about them).

For those who are already familiar with psychopharmacology, this book should provide easy reading from beginning to end. Going back and forth between the text and the graphics should provide interaction. Following review of the complete text, it should be simple to review the entire book by going through the graphics once again.

The text is purposely written at a conceptual level rather than a pragmatic level and includes ideas that are simplifications and rules, while sacrificing precision and discussion of exceptions to rules. Thus, this is not a text intended for the sophisticated subspecialist in psychopharmacology.

One other limitation of the book is that it is not extensively referenced to original papers but rather to textbooks and reviews, including several of the author's.

For those interested in the specific updates made in the second edition, the first section on basic science has expanded coverage of gene expression and transcription factors; of developmental neurobiology, neuronal selection, synaptogenesis, and growth factors; of the complex genetics of psychiatric disorders; and of new concepts of neurodegeneration such as apoptosis, with dozens of new color graphics.

The second section on clinical science has been increased by two chapters to accommodate the increase in the numbers of drugs and advances in knowledge about psychiatric disorders. Three new neurotransmitter systems are introduced and illustrated: substance P and the neurokinin family; nitric oxide; and the endocannabi-noids such as anandamide (the "brain's own marijuana"). Also amplified is coverage of the classical neurotransmitter systems, especially intercommunications now illustrated between serotonin and dopamine and between norepinephrine/noradrenaline and serotonin. Also included are numerous new illustrations of noradrenergic and cholinergic pathways.

In the clinical syndrome chapters, there is now coverage of several new topics, including bipolar disorders, attention deficit disorder, erectile dysfunction, the role of estrogen in mood and cognitive disorders across the female life cycle, disorders in children and adolescents (in part), and pharmacokinetics of psychopharmacologic drugs. Some sections have been revised, including those on sleep disorders, and schizophrenia and psychotic disorders. In the clinical therapeutics chapters, the explosion of new therapeutics is reflected by the inclusion of over 30 new icons for drugs that appear for the first time in the second edition, including new anti-

depressants, mood stabilizers, atypical antipsychotics, acetylcholinesterase inhibitors, phosphodiesterase inhibitors, sedative hypnotics, and several others.

I would be remiss if I did not thank my editors at Cambridge University Press for their most helpful suggestions and exhortations to get this edition in on time.

Best wishes for your first step on your journey into this fascinating field of psychopharmacology.

STEPHEN M. STAHL, M.D., Ph.D.

CONTENTS

CHAPTER 1

PRINCIPLES OF CHEMICAL NEUROTRANSMISSION

Modern psychopharmacology is largely the story of chemical neurotransmission. To understand the actions of drugs on the brain, to grasp the impact of diseases on the central nervous system (CNS), and to interpret the behavioral consequences of psychiatric medicines, one must be fluent in the language and principles of chemical neurotransmission. The importance of this fact cannot be overstated for the student of psychopharmacology. What follows in this chapter will form the foundation for the entire book and the roadmap for one's journey through one of the most exciting topics in science today, namely the neuroscience of how drugs act on the CNS.

The Synapse

The best understood chemical neurotransmission occurs at synapses, specialized sites that connect two neurons. Neurons are organized so that they can both send synaptic

information to other neurons and receive synaptic information from other neurons. Figure 1 — 1 is an artist's concept of how a neuron is organized in order to *send* synaptic information. This is accomplished by a long *axon* branching into terminal fibers ready to make synaptic contact with other neurons. Figure 1—2, by contrast, shows how a neuron is organized to *receive* synaptic information on its dendrites, cell body, and axon. The synapse itself is enlarged conceptually in Figure 1 — 3, showing its specialized structure, which enables chemical neurotransmission to occur.

Three Dimensions of Neurotransmission

Chemical neurotransmission can be described in three dimensions: space, time and function.

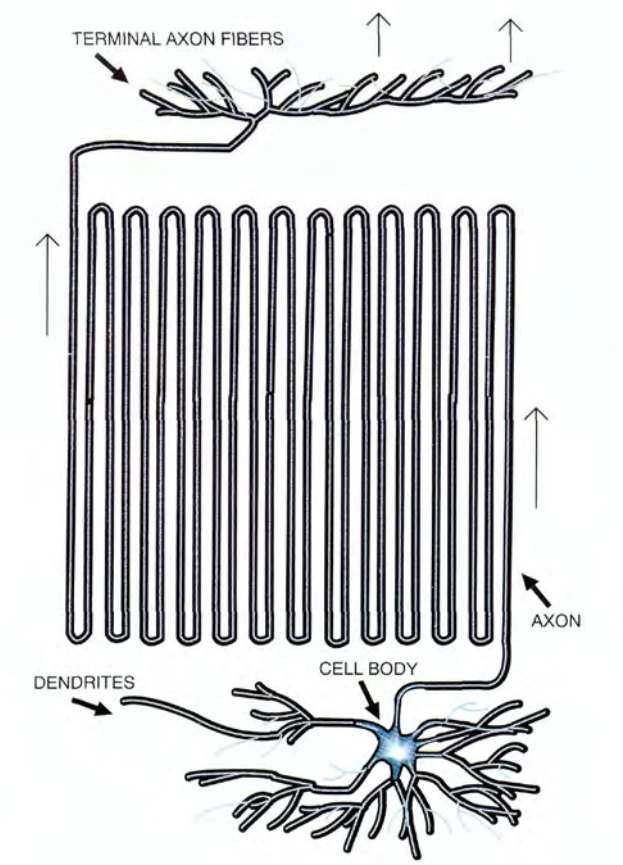

FIGURE 1 — 1. This is an artist's concept of how a neuron is organized in order to **send** synaptic information. It does this via a long axon, which sends its information into numerous branches called **terminal axon fibers**. Each of these axon terminals can potentially make presynaptic contacts with other neurons. Also shown is the **cell body**, which is the command center of the nerve, contains the nucleus of the cell, and processes both incoming and outgoing information. The **dendrites** are organized largely to capture information from other neurons (see also Fig. 1—2).

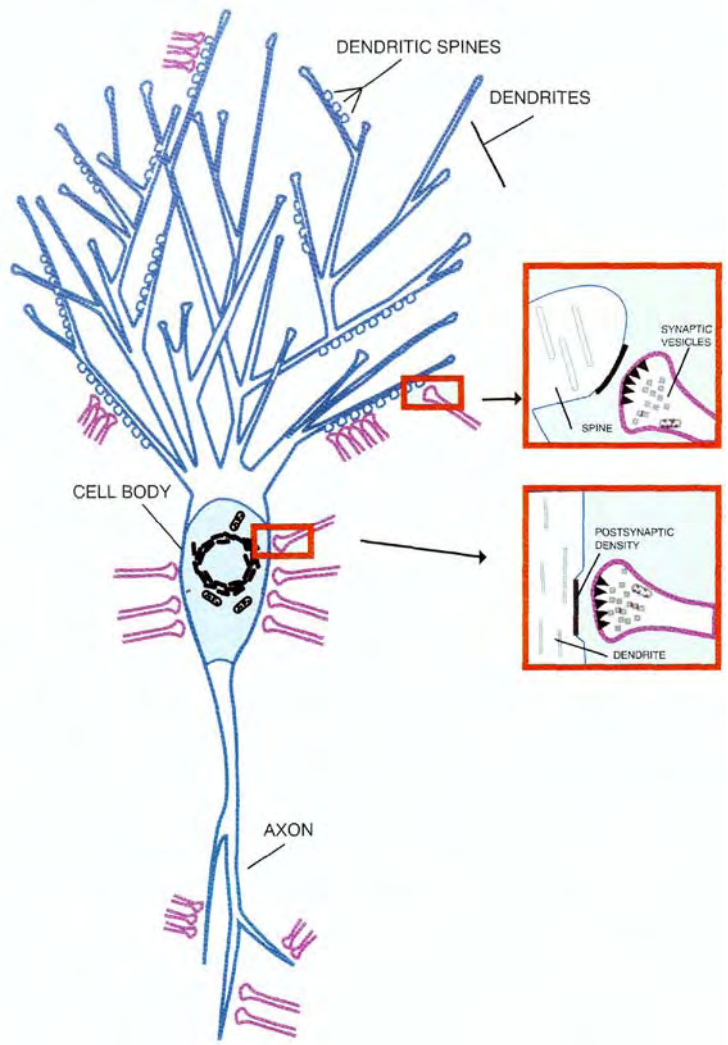

FIGURE 1—2. This figure shows how a neuron is organized to **receive** synaptic information. Presynaptic input from other neurons can be received postsynaptically at many sites, but especially on **dendrites**, often at specialized structures called **dendritic spines.** Other postsynaptic neuronal sites tor receiving presynaptic input from other neurons include the **cell body** and **axon terminal.**

Space: The Anatomically Addressed Nervous System

Classically, the central nervous system has been envisioned as a series of "hard-wired" synaptic connections between neurons, not unlike millions of telephone wires within thousands upon thousands of cables (Fig. 1—4). This idea has been referred to as the "anatomically addressed" nervous system. The anatomically addressed brain is thus a complex wiring diagram, ferrying electrical impulses to wherever the "wire" is plugged in (i.e., at a synapse). There are an estimated 100 billion neurons, which make over 100 trillion synapses, in a single human brain.

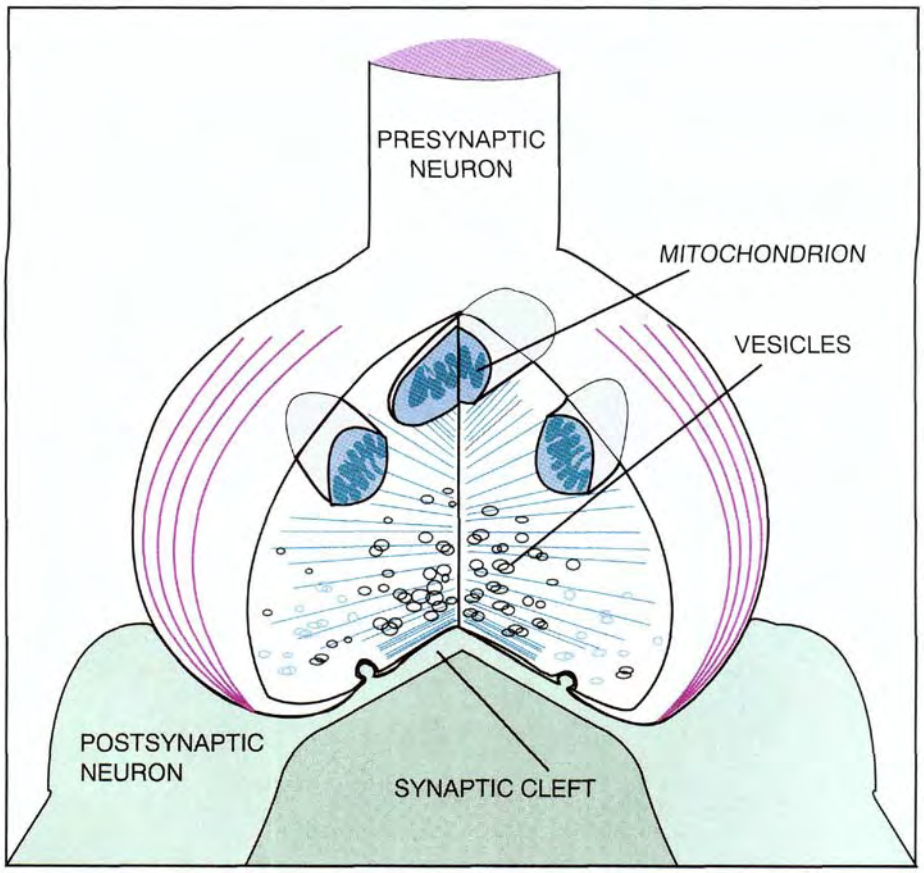

FIGURE 1-3. The synapse is enlarged conceptually here showing its specialized structures that enable chemical neurotransmission to occur. Specifically, a **presynaptic neuron** sends its **axon terminal** to form a synapse with a **postsynaptic neuron**. Energy for this process is provided by mitochondria in the presynaptic neuron. Chemical neurotransmitter is stored in small vesicles ready for release on firing of the presynaptic neuron. The **synaptic cleft** is the connection between the presynaptic neuron and the postsynaptic neuron. Receptors are present on both sides of this cleft and are key elements of chemical neurotransmission.

Neurons send electrical impulses from one part of the cell to another part of the same cell via their axons, but these electrical impulses do not jump directly to other neurons. Neurons communicate by one neuron hurling a chemical messenger, or neurotransmitter, at the receptors of a second neuron. This happens frequently, but not exclusively, at the sites of synaptic connections between them (Fig. 1 — 3). Communication *between* neurons is therefore chemical, not electrical. That is, an electrical impulse in the first neuron is converted to a chemical signal at the synapse between it and a second neuron, in a process known as chemical neurotransmission. This occurs predominantly in one direction, from the presynaptic axon terminal, to any of a variety of sites on a second postsynaptic neuron. However, it is increasingly apparent that the postsynaptic neuron can also "talk back" to the presynaptic neuron with chemical messengers of its own, perhaps such as the neurotransmitter nitric oxide. The frequency and extent of such cross-communication may determine how

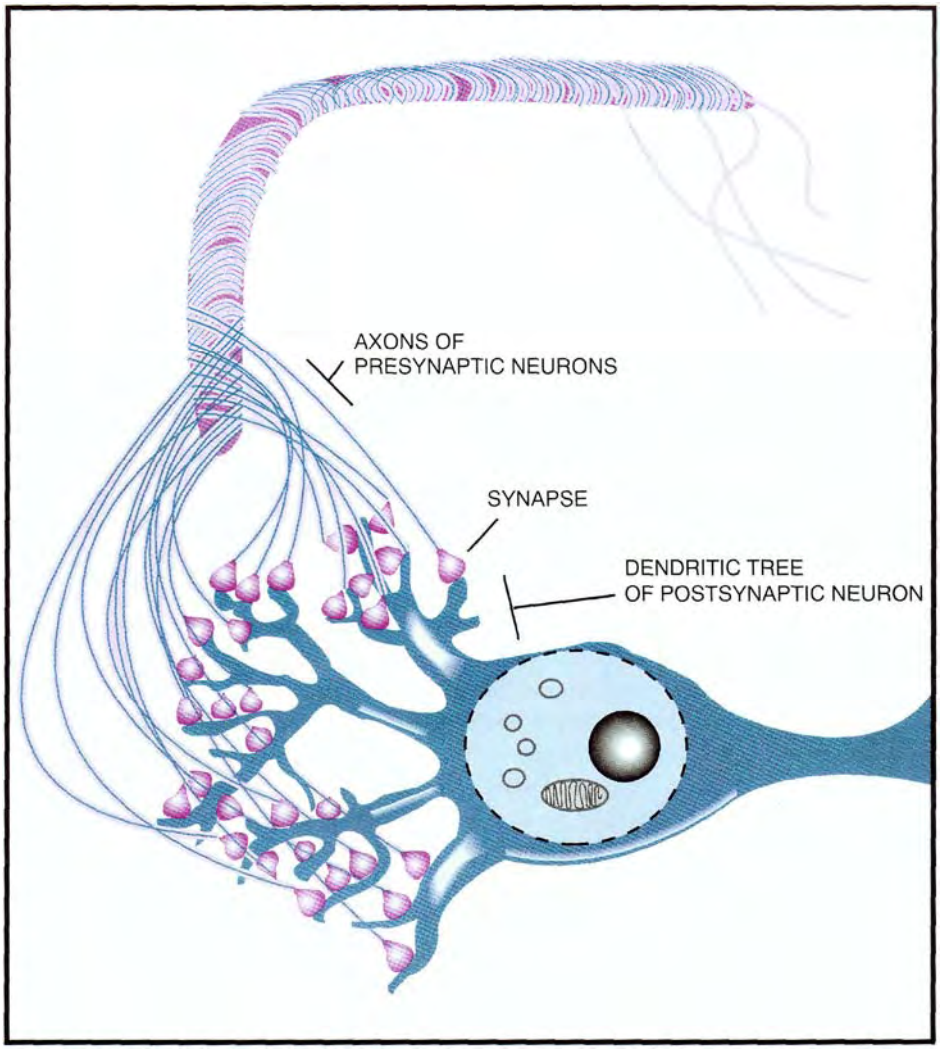

FIGURE 1 -4. The **anatomically addressed nervous system** is the concept that the brain is a series of hard-wired connections between neurons, not unlike millions of telephone wires within thousands and thousands of cables. Shown in the figure is a cable of axons from many different neurons, all arriving to form synaptic connections with the dendritic tree of the postsynaptic neuron.

well that synapse functions. Thus, mental "exercise" may provoke progressive structural changes at a synapse, which increase the ease of neurotransmission there (Fig. 1-3).

Space: The Chemically Addressed Nervous System

More recently, neurotransmission without a synapse has been described, which is called *volume neurotransmission* or nonsynaptic diffusion neurotransmission. Chemical messengers sent by one neuron to another can spill over to sites distant to the synapse by diffusion. Thus, neurotransmission can occur at any compatible receptor within

the diffusion radius of the neurotransmitter, not unlike modern communication with cellular telephones, which function within the transmitting radius of a given cell (Fig. 1 — 5). This concept is called the *chemically addressed* nervous system, where neurotransmission occurs in chemical "puffs." The brain is thus not only a collection of wires but also a sophisticated "chemical soup." The chemically addressed nervous system is particularly important in understanding the actions of drugs that act at various neurotransmitter receptors, since such drugs will act wherever there are relevant receptors and not just where such receptors are innervated with synapses by the anatomically addressed nervous system.

Time: Fast-Onset versus Slow-Onset Signals

Some neurotransmitter signals are very fast in onset, starting within milliseconds of receptors being occupied by neurotransmitter. Two of the best examples of fast-onset signals are those caused by the neurotransmitters glutamate and gamma-aminobutyric acid (GABA). Glutamate is a neurotransmitter that universally stimulates almost any neuron, whereas GABA is a messenger that universally inhibits almost any neuron (Fig. 1—6). Both of these neurotransmitters can cause fast onset of chemical signaling by rapidly changing the flux of ions, thus altering within milliseconds the excitability of the neuron.

On the other hand, signals from other neurotransmitters can take longer to develop, ranging from many milliseconds to even several full seconds of time. Sometimes these neurotransmitters with slower onset are called neuromodulators, since slow-onset ionic signals may last long enough to carry over and modulate a subsequent neurotransmission by another neurotransmitter (Fig. 1—6). Thus, a slow-onset but long-acting neuromodulating signal can set the tone of a neuron and influence it not only by a primary action of its own, but also by a modifying action on the neurotransmission of a second chemical message sent before the first signal is gone. Examples of slow-onset, long-acting neurotransmitters are the monoamines norepi-nephrine and serotonin, as well as various neuropeptides. Although their signals can take seconds to develop, the biochemical cascades that they trigger can last for days.

Function: Presynaptic Events

The third dimension of chemical neurotransmission is function, namely that cascade of molecular and cellular events set into action by the *chemical signaling* process. First come the presynaptic and then the postsynaptic events. An electrical impulse in the first, or presynaptic, neuron is converted into a chemical signal at the synapse by a process known as *excitation-secretion coupling.*

Once an electrical impulse invades the presynaptic axon terminal, it causes the release of chemical neurotransmitter stored there (Fig. 1—3). Electrical impulses open ion channels, such as *voltage-gated calcium channels* and *voltage-gated sodium channels,* by changing the ionic charge across neuronal membranes. As calcium flows into the presynaptic nerve, it anchors the synaptic vesicles to the inner membrane of the nerve terminal so that they can spill their chemical contents into the synapse. The way is paved for chemical communication by previous synthesis and storage of neurotransmitter in the first neuron's presynaptic axon terminal.

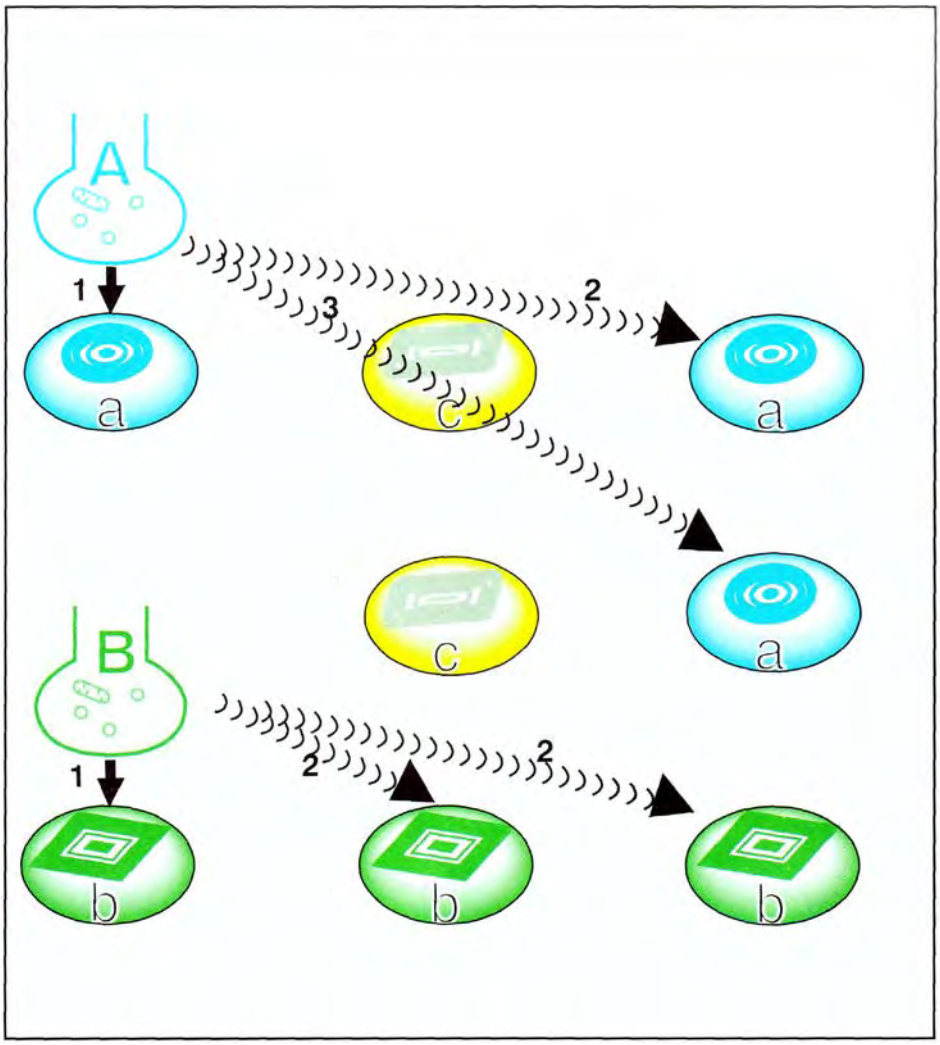

FIGURE 1 — 5. A conceptualization of the **chemically addressed nervous system** is shown. Two anatomically addressed synapses (neurons A and B) are shown communicating *(arrow 1)* with their corresponding postsynaptic receptors *(a* and *b).* However, there are also receptors for neurotransmitter a, neurotransmitter *b,* and neurotransmitter *c,* which are distant from the synaptic connections of the anatomically addressed nervous system. If neurotransmitter *A* can diffuse away from its synapse before it is destroyed, it will be able to interact with other receptor a sites distant from its own synapse *(arrow 2).* If neurotransmitter *A* encounters a different receptor not capable of recognizing it (receptor c), it will not interact with that receptor even if it diffuses there *(arrow* 3). Thus, a chemical messenger sent by one neuron to another can spill over by diffusion to sites distant from its own synapse. Neurotransmission can occur at a compatible receptor within the diffusion radius of the matched neurotransmitter. This is analogous to modern communication with cellular telephones, which function within the transmitting radius of a given cell. This concept is called the **chemically addressed** nervous system, in which neurotransmission occurs in chemical "puffs." The brain is thus not only a collection of wires (Fig. 1—2 and the anatomically addressed nervous system), but also a sophisticated "chemical soup" (Fig. 1-3 and the chemically addressed nervous system).

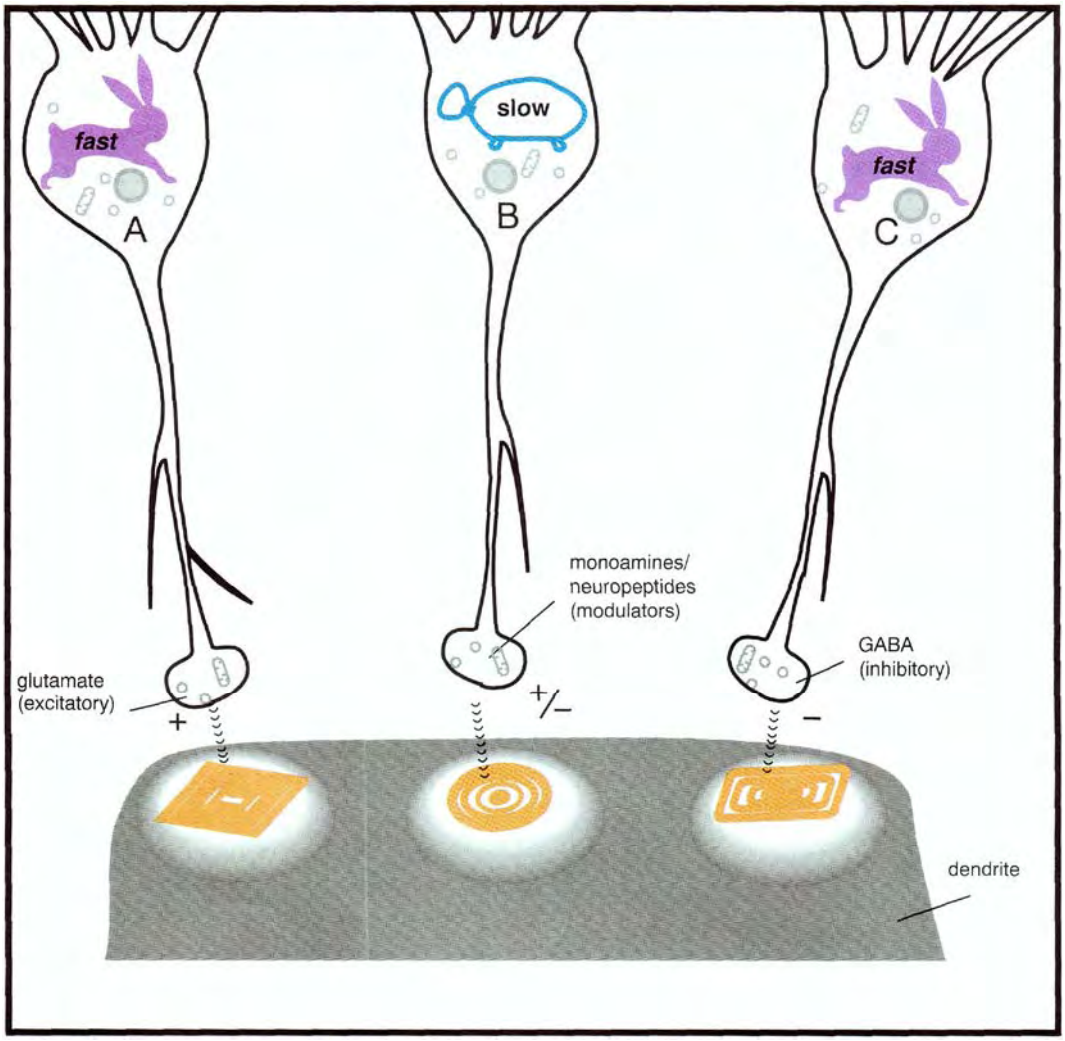

FIGURE 1-6. Some neurotransmitter signals are **fast** in onset (rabbit/hare neurons *A* and *C)* whereas other transmitter signals are **slow** in onset (tortoise neuron *B).* The neurotransmitter **glutamate** (neuron A) is fast in onset and **excitatory** (+), whereas the neurotransmitter **GABA** (neuron *C)* is fast on onset and **inhibitory** (—). In contrast to the fast glutamate and GABA signals, neurotransmission following those neurotransmitters known as **monoamines** or **neuropeptides** tends to be slow in onset (neuron *B)* and either excitatory (+) or inhibitory (—). Fast in this context is a few milliseconds, whereas slow signals are many milliseconds or even several full seconds of time. Slower-onset neurotransmitters may nevertheless be long-acting. They are sometimes called **neuromodulators**, since they may modulate a different signal from another neurotransmitter. In this figure, three neurons (A, *B,* and *C)* are all transmitting to a postsynaptic dendrite on the same neuron. If the slow signal from *B* is still present when a fast signal from *A* or *C* arrives, the *B* signal will modulate the *A* or *C* signal. Thus, a long-acting neuromodulating signal of neuron *B* can set the tone of the postsynaptic neuron, not only by a primary action of its own but also by modifying the action of neurons *A* and *C.*

When presynaptic neurons use monoamine neurotransmitters, they manufacture not only the monoamine neurotransmitters themselves but also the *enzymes* for monoamine synthesis (Fig. 1—7), the *receptors* for monoamine reuptake and regulation (Fig. 1—8) and the *synaptic vesicles* loaded with monoamine neurotransmitter. They do this on receiving instructions from the "command center" or headquarters, namely the cell nucleus containing the neuron's deoxy-ribonucleic acid (DNA). These activities occur in the cell body of the neuron, but then monoamine presynaptic neurons send all of these items to the presynaptic nerve terminals, which act as "field offices" for that neuron throughout the brain (Figs. 1 — 1 to 1—3, 1—7, 1—8). Neurotransmitter is thus packaged and stored in the presynaptic neuron in vesicles, like a loaded gun ready to fire.

Since the enzyme machinery to manufacture more monoamines is present in axon terminals (Fig. 1—7), additional monoamine neurotransmitters can be synthesized there. Since a reuptake pump, which can recapture released monoamines, is present on the presynaptic neuron (Fig. 1—8), monoamines used in one neurotransmission can be captured for reuse in a subsequent neurotransmission. This is in contrast to the way in which neuropeptides function in neurotransmission (Fig. 1—9).

In the case of neuropeptides, presynaptic neurotransmission synthesis occurs only in the *cell body* because the complex machinery for neuropeptide synthesis is *not* transported into the axon terminal. Synthesis of a specific neuropeptide begins with the *pre-propeptide gene* in the cell nucleus (Fig. 1—9). This gene is transcribed into primary ribonucleic acid (RNA), which can be rearranged, or "edited," to create different versions of RNA, known as alternative splice variants, such as pre-propeptide RNA.

Next, this RNA is translated into a pre-propeptide, which enters the endoplasmic reticulum (Fig. 1—9). This is the "precursor of a precursor," sometimes also called the "grandparent" of the neuropeptide neurotransmitter. This pre-propeptide grand-parent neuropeptide has a peptide "tail," called a signal peptide, which allows the pre-propeptide to enter the endoplasmic reticulum, where the tail is clipped off by an enzyme called a signal peptidase with formation of the propeptide, or "parent" of the neuropeptide. The propeptide is the direct precursor of the neuropeptide neurotransmitter itself.

This parental propeptide then leaves the endoplasmic reticulum and enters synaptic vesicles, where it is finally converted into the neuropeptide itself by a converting enzyme located there. Since only the synaptic vesicles loaded with neuropeptide neurotransmitters and not the synthetic enzyme machinery to make more neuropeptides, are transported down to the axon terminals, no local synthesis of more neuropeptide neurotransmitter can occur in the axon terminal.

Furthermore, there does not appear to be any significant reuptake pump for neuropeptides, so once they are released, they are not recaptured for subsequent reuse (Fig. 1—9). The action of peptides is terminated by catabolic peptidases, which cut the peptide neurotransmitter into inactive metabolites.

Function: Post synaptic Events

Once neurotransmitter has been fired from the presynaptic neuron, it shoots across the synapse, where it seeks out and hits target sites on receptors of the postsynaptic neuron that are very selective for that neurotransmitter. (This will be discussed in

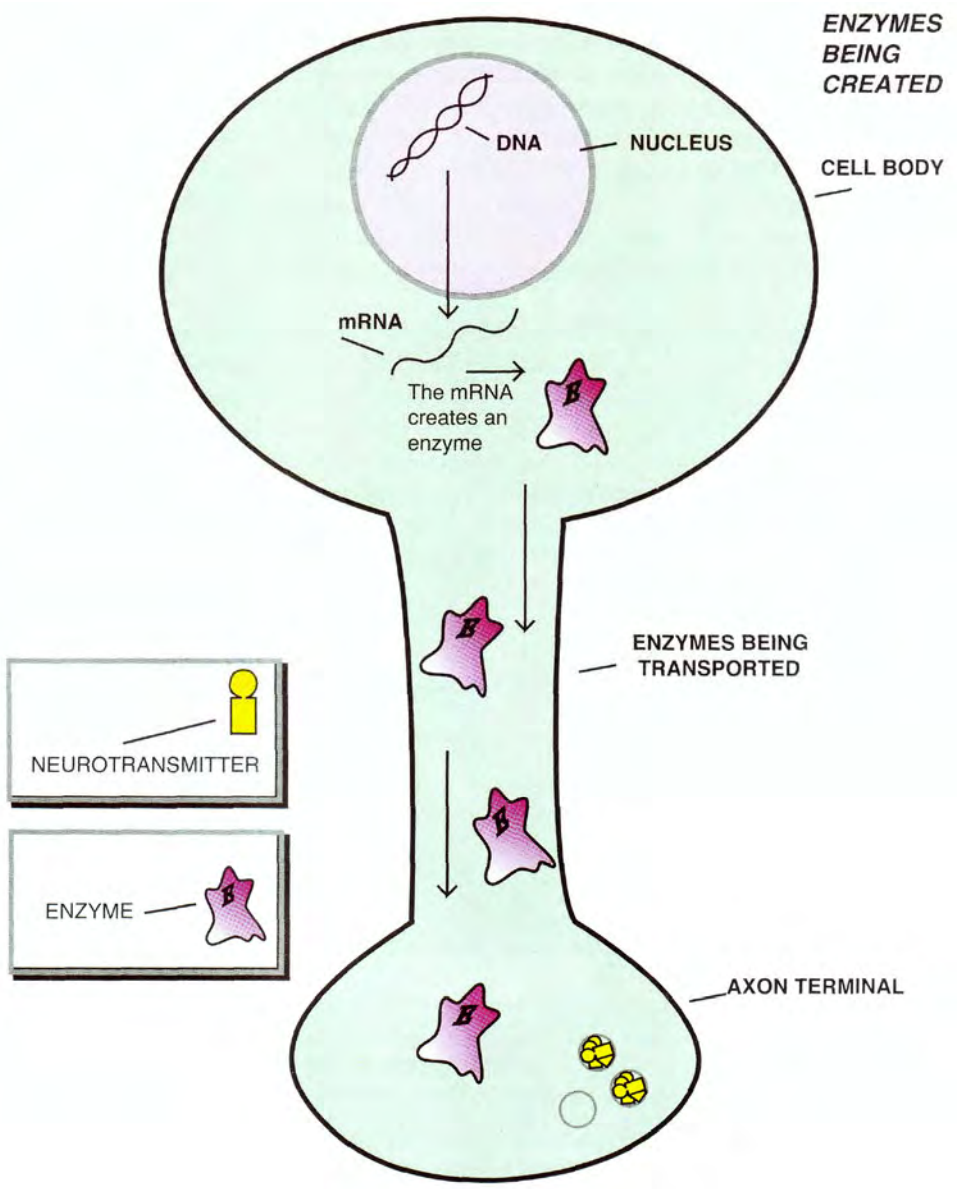

FIGURE 1—7. Shown here is the axonal transport of monoamine-synthesizing enzymes in a monoaminergic neuron. Enzymes are protein molecules, which are **created** (synthesized) in the **cell body**, starting in the cell **nucleus.** Once synthesized, enzymes may be **transported** down the axon to the **axon terminal** to perform functions necessary for neurotransmission, such as making or destroying neurotransmitter molecules. **DNA** in the cell nucleus is the "command center," where orders to carry out the synthesis of enzyme proteins are executed. DNA is a template for **mRNA** synthesis, which in turn is a template for protein synthesis in order to form the enzyme by classical molecular rules.

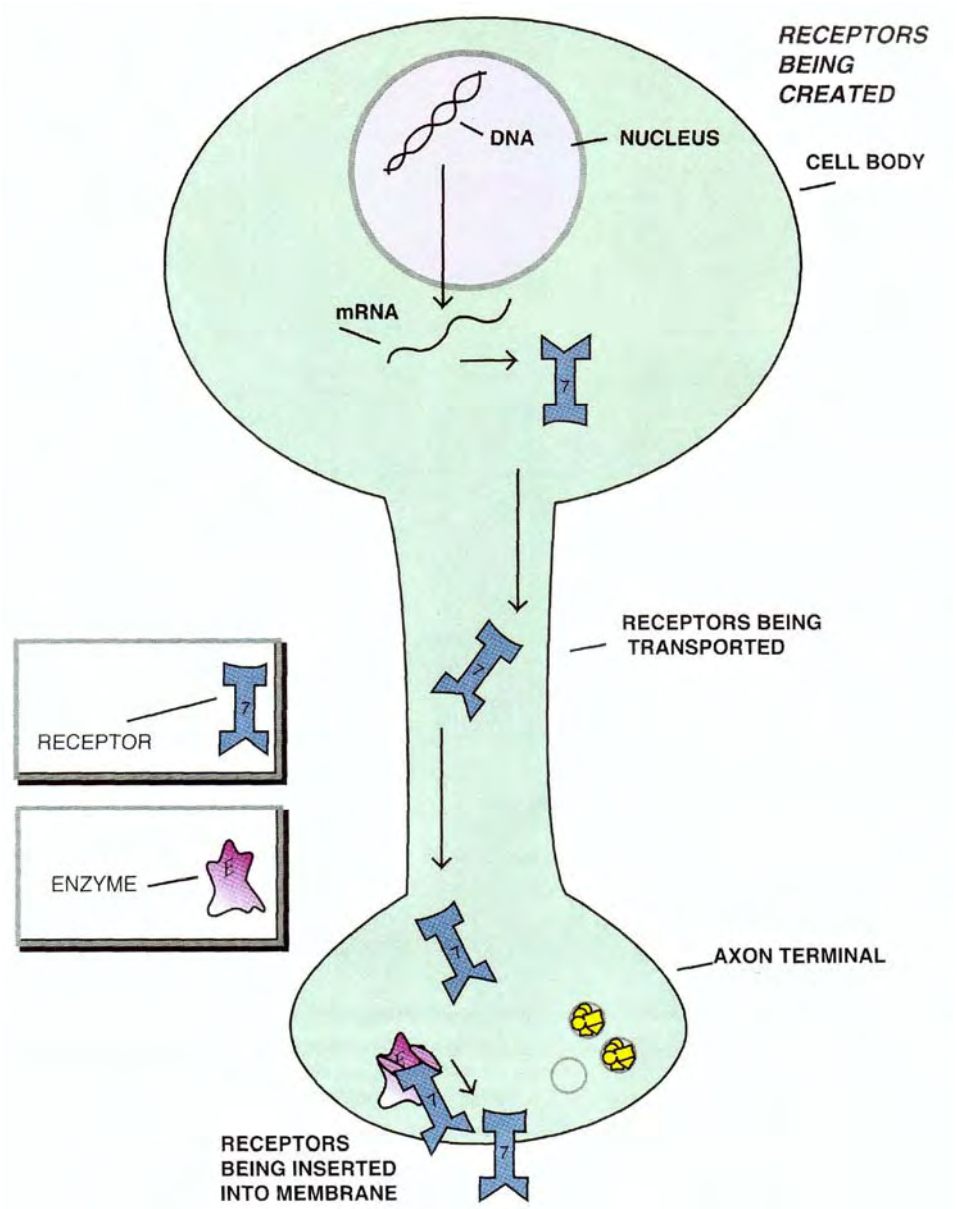

FIGURE 1—8. Shown here is the axonal transport of a presynaptic receptor in a monoaminergic neuron. In analogy with the process shown in Figure 1-7, **receptors** are also protein molecules **created** (synthesized) in the **cell body** of the neuron. Receptors can also be **transported** to various parts of the neuron, including the **axon terminal,** where they can be **inserted** into neuronal membranes to perform various functions during neurotransmission, such as capturing and reacting to neurotransmitters released from incoming signals sent by neighboring neurons.

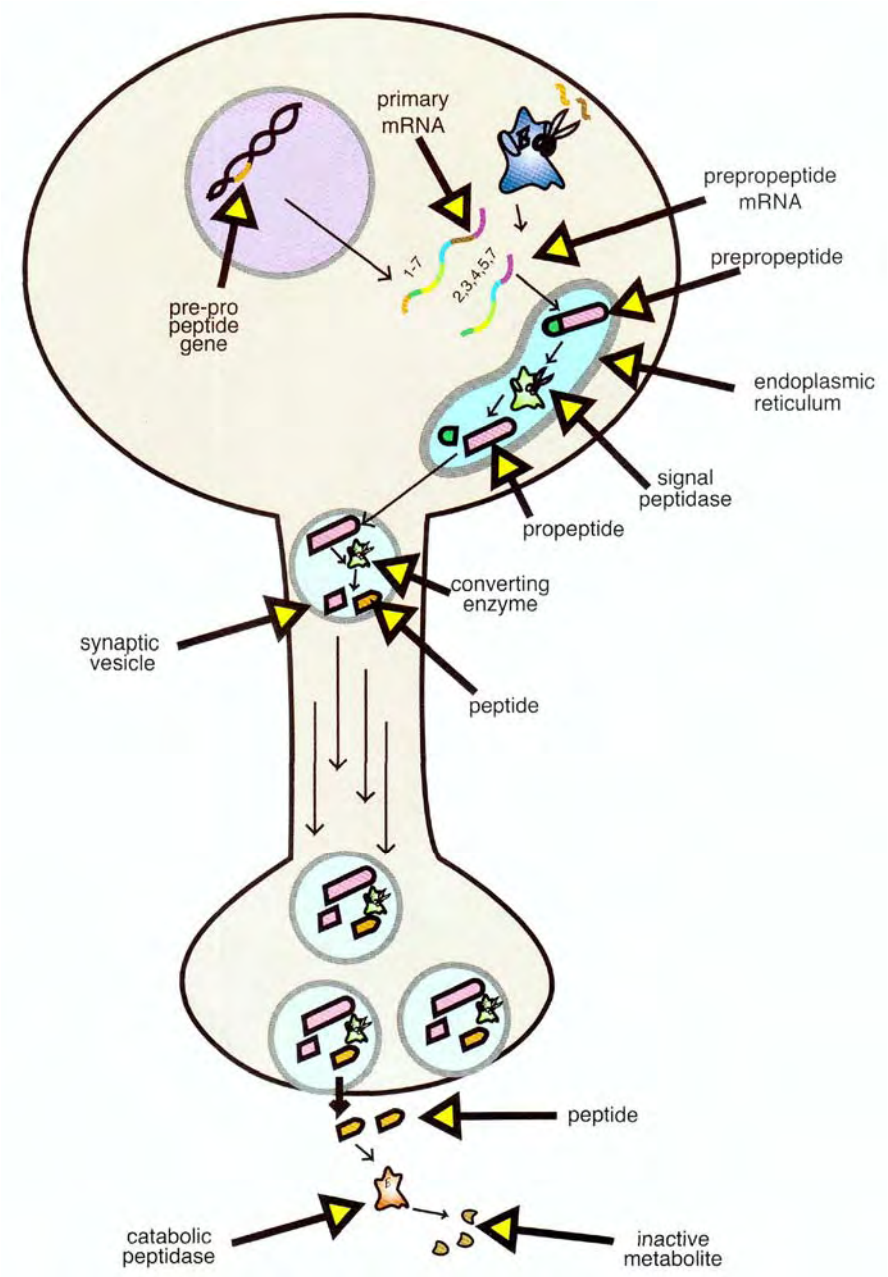

FIGURE 1—9. Neurotransmitter synthesis in a neuropeptidergic neuron. Neurotransmitter synthesis occurs only in the **cell body** because the complex machinery for neuropeptide synthesis is not transported into the axon terminal. Synthesis of a specific neuropeptide begins with the transcription of the pre-propeptide gene in the cell nucleus into primary RNA, which can be rearranged or "edited" to create different versions of RNA, known as alternative splice variants or **pre-propeptide RNA**. Next, RNA is translated into a **pre-propeptide**, which enters the endoplasmic reticulum, where its peptide tail is clipped off by an enzyme called a signal peptidase to form the propeptide, the direct precursor of the neuropeptide neurotransmitter. Finally, the propeptide enters synaptic vesicles, where it is converted into the **neuropeptide** itself. Synaptic vesicles loaded with neuropeptide neurotrans-mitters are transported down to the axon terminals, where there is no reuptake pump for neuropep-tides. The action of peptides is terminated by catabolic peptidases, which cut the peptide neurotransmitter into inactive metabolites.

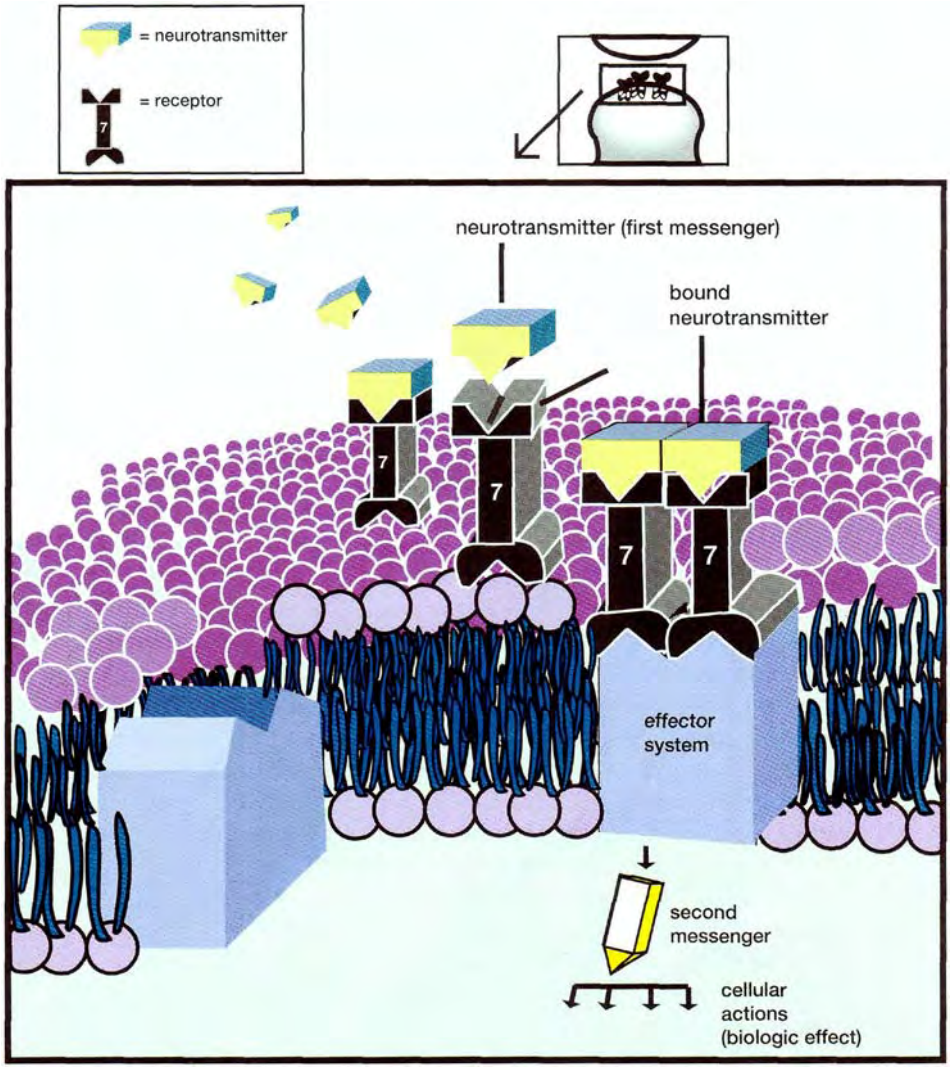

FIGURE 1 — 10. The functional outcome of neurotransmission is depicted here in the postsynaptic neuron. **Neurotransmitter** released from the presynaptic neuron is considered the **first messenger**. It binds to its **receptor** and the **bound neurotransmitter** causes an **effector system** to manufacture a **second messenger**. That second messenger is inside the cell of the postsynaptic neuron. It is this second messenger that then goes on to create **cellular actions** and **biological effects**. Examples of this are the neuron beginning to synthesize a chemical product changing its firing rate. Thus, information in the presynaptic neuron is conveyed to the postsynaptic neuron by a chain of events. This is how the brain is envisioned to do its work—thinking, remembering, controlling movement, etc. — through the synthesis of brain chemicals and the firing of brain neurons.

much greater detail in the section below on molecular neurobiology and in Chapters 2, 3, and 4). Receptor occupancy by neurotransmitter binding to highly specific sites begins the postsynaptic events of chemical neurotransmission (Fig. 1 — 10). This process is very similar to the binding of substrates by enzymes at their active sites. The neurotransmitter acts as a key fitting the receptor lock quite selectively.

Classically, it has been held that this neurotransmitter-receptor complex initiates a process that reconverts the chemical message back into an electrical impulse in the second nerve. This is certainly true for rapid-onset neurotransmitters and can explain the initial actions of some slow-onset neurotransmitters as well. However, it is now known that the postsynaptic neuron has a vast repertoire of responses beyond)ust whether it changes its membrane polarization to make it more or less likely to "fire." Indeed, many important biochemical processes are triggered in the postsynaptic neuron by neurotransmitters occupying their receptors. Some of these begin within milliseconds, whereas others can take days to develop (Figs. 1 — 11 to 1 — 13).

Thus, chemical neurotransmission in the postsynaptic neuron begins with receptor occupancy by the neurotransmitter, the *first messenger*. This leads to numerous intracellular events, starting with additional messengers within the cell (Fig. 1 — 10). The *second messenger* is an intracellular chemical, which is created by the first messenger neurotransmitter occupying the receptor outside of the cell, in the synaptic connection between the first and the second neuron. The best examples of second messengers are cyclic adenosine monophosphate (cAMP) and phosphatidyl inositol. Some receptors are linked to one type of second messenger and others to different second messengers.

The second messenger intracellular signal eventually tells the second neuron to change its ionic fluxes, to propagate or disrupt neuronal electrical impulses, to phosphorylate intracellular proteins, and to perform many, many other actions. It does this by a biochemical cascade, which eventually reaches the cell nucleus and results in genes being turned on or turned off (Fig. 1 — 11). Once gene expression is so triggered, a second biochemical cascade based on the direct consequences of which specific genes have been turned on or off is initiated (Fig. 1 — 12). Many of these events are still mysteries to neuroscientists. These events of postsynaptic neurotransmission are akin to a molecular "pony express" system, with the chemical information encoded within a neurotransmitter-receptor complex being passed along from molecular rider to molecular rider until the message is delivered to the appropriate DNA mailbox in the postsynaptic neuron's genome (Fig. 1 — 11).

Thus, the function of chemical neurotransmission is not so much to have a presynaptic neurotransmitter communicate with its postsynaptic receptors as to have a *presynaptic genome converse with a postsynaptic genome:* DNA to DNA; presynaptic command center to postsynaptic command center.

In summary, the message of chemical neurotransmission is transferred via three sequential molecular pony express routes: (1) a presynaptic neurotransmitter synthesis route from the presynaptic genome to the synthesis and packaging of neurotransmitter and supporting enzymes and receptors (Figs. 1—7, 1—8, and 1—9); (2) a postsynaptic route from receptor occupancy through second messengers (Fig. 1 — 10) all the way to the genome, which turns on postsynaptic genes (Fig. 1 — 11); and (3) another postsynaptic route, starting from the newly expressed postsynaptic genes transferring information as a molecular cascade of biochemical consequences throughout the postsynaptic neuron (Fig. 1 — 12).

It should now be clear that neurotransmission does not end when a neurotransmitter binds to a receptor or even when ion flows have been altered or second messengers have been created. Events such as these all start and end within milliseconds to seconds following release of presynaptic neurotransmitter (Fig. 1 — 13). The ultimate goal of neurotransmission is to alter the biochemical activities of the

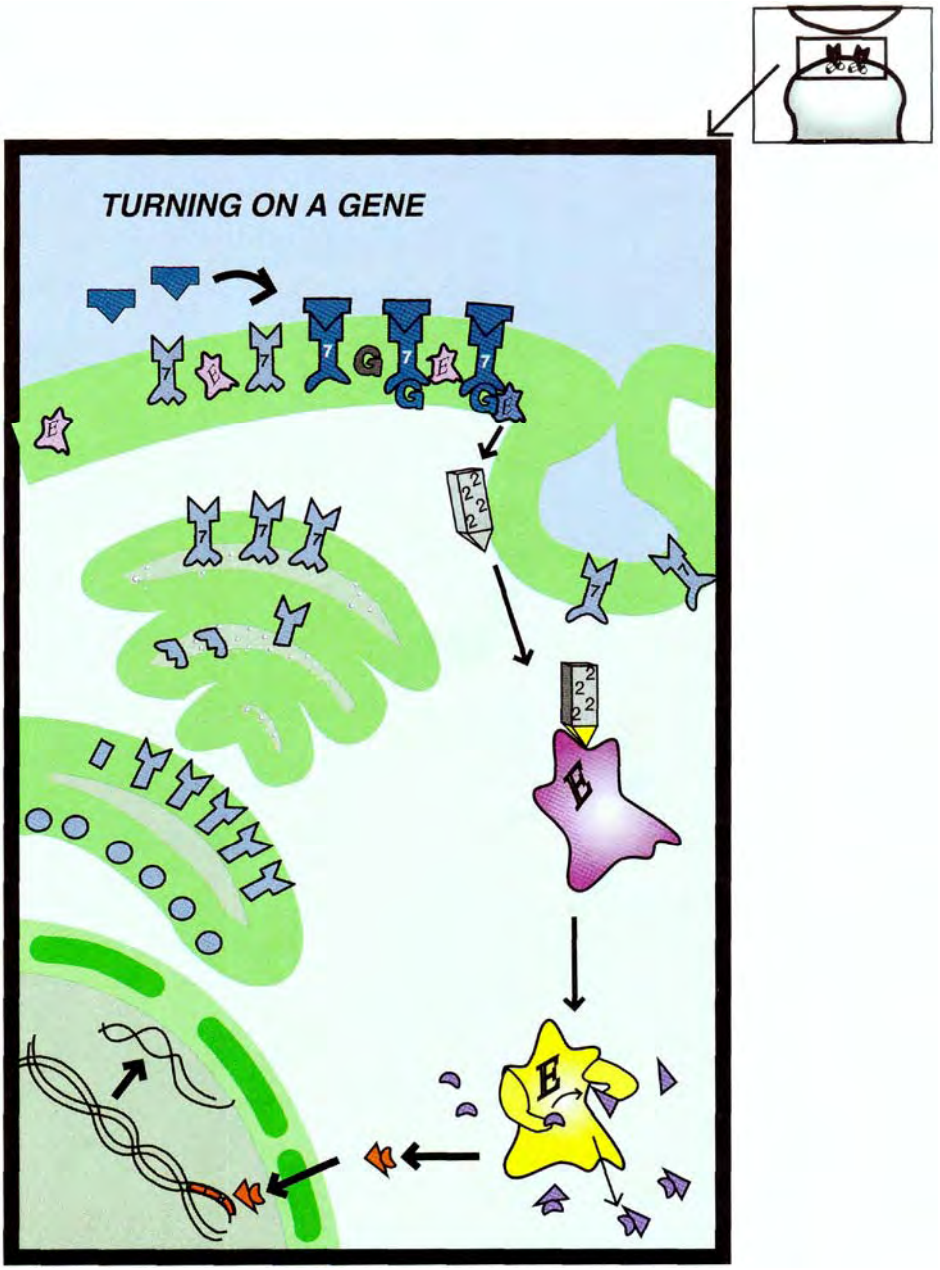

FIGURE 1 — 11. Shown here is a neurotransmitter setting off a cascade that results in turning on a gene. The neurotransmitter binds to its receptor at the top, creating a second messenger. The second messenger activates an intracellular enzyme, which results in the creation of transcription factors *(red arrowheads)* that cause gene activation (red DNA segment).

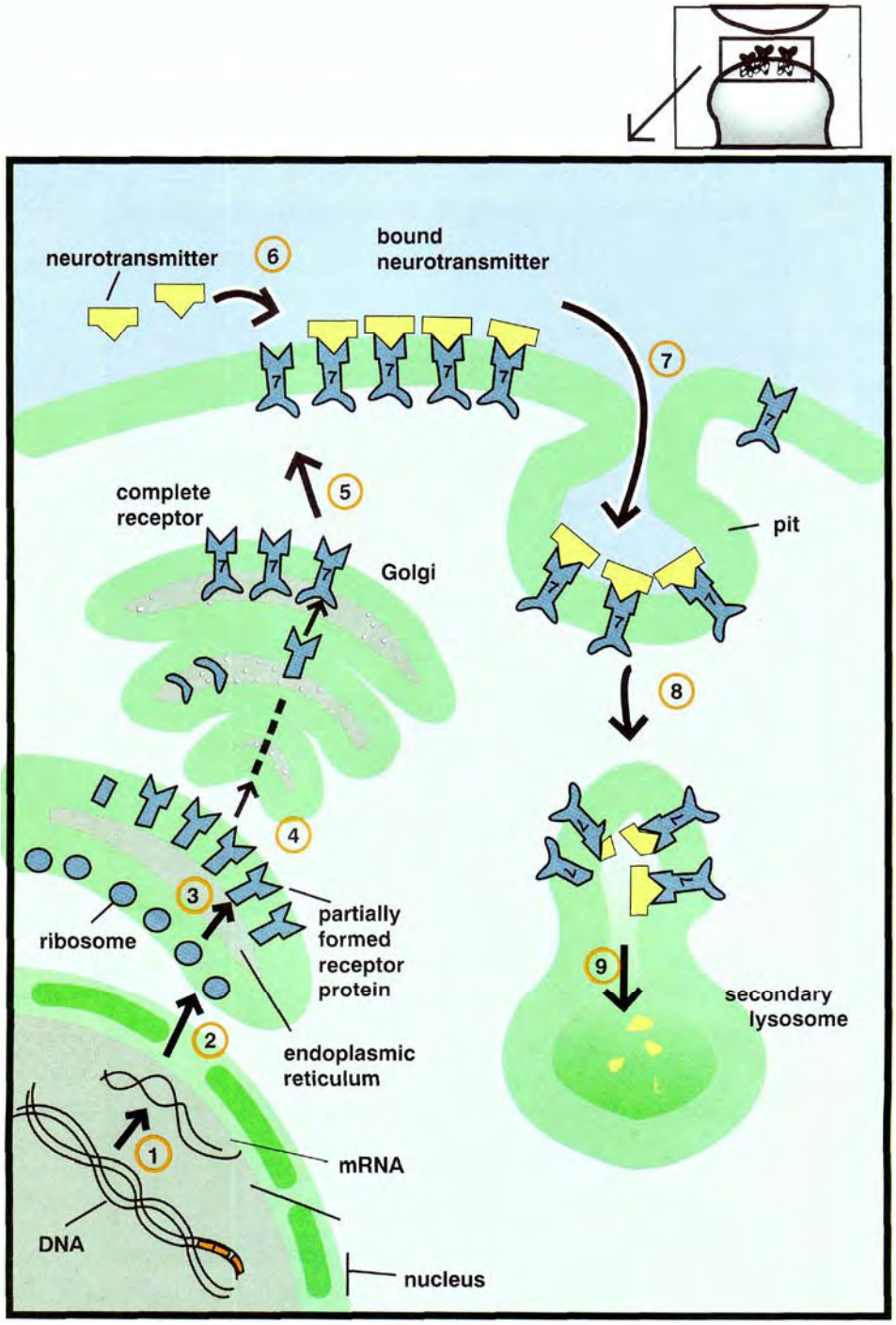

FIGURE 1-12. As in Figures 1-7 to 1-9, DNA in the cell nucleus is the "command center," where orders to carry out the synthesis of receptor proteins are executed. DNA is a template for **mRNA** synthesis, which in turn is a template for protein synthesis in order to form the receptor by classical molecular rules. Shown in this figure is the molecular neurobiology of receptor synthesis. The process begins in the cell nucleus, when a gene (red DNA segment) is transcribed into messenger RNA

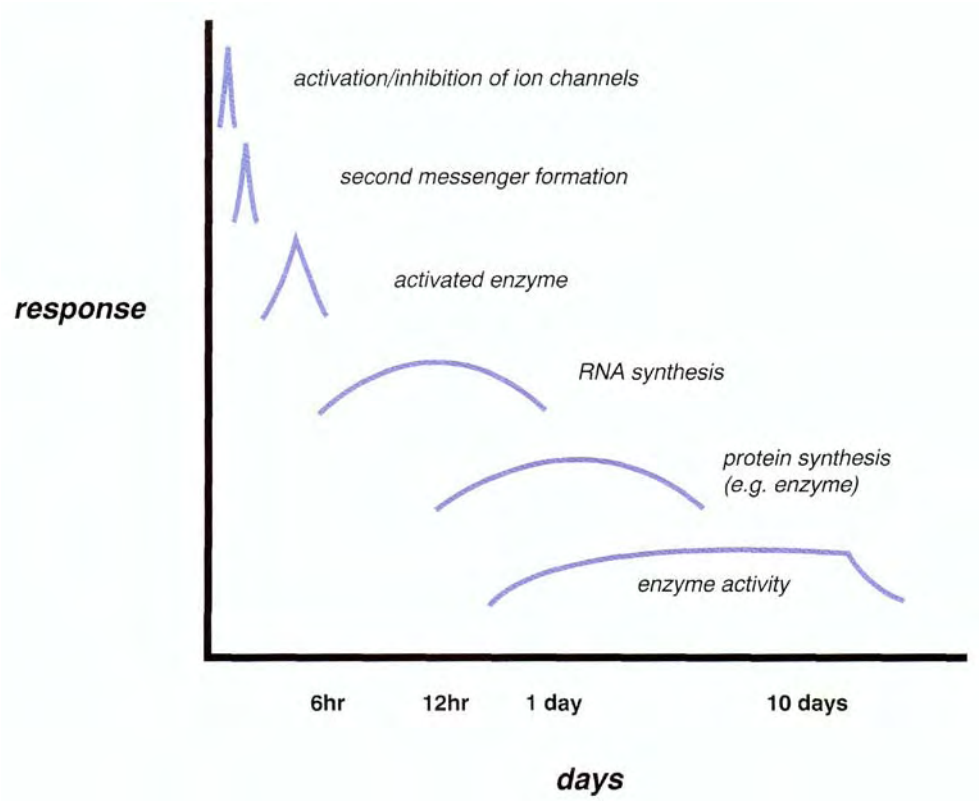

FIGURE 1-13. The time course of postsynaptic responses to presynaptic neurotransmitter are shown here. At the top, the most immediate actions are on **ion channels** or **second messenger formation**. Next comes **activation of intracellular enzymes**, leading to transcription of genes into **RNA synthesis**. This leads naturally to translation of RNA into **proteins**. Proteins have functions, which include such actions as **enzyme activity**. By the time enzyme activity has begun, it is already hours after the initial neurotransmission event. Once so activated, the functional changes in enzyme activity can last for many days. Thus, the ultimate effects of neurotransmission are not only delayed but long-lasting.

(arrow 1). Messenger RNA then travels to the endoplasmic reticulum *(arrow* 2), where ribosomes cause the messenger RNA to be translated into partially formed receptor protein *(arrow* 3). The next step

is for partially formed receptor protein to be transformed into complete receptor molecules in the golgi apparatus *(arrow 4).* Completely formed receptor molecules are proteins and these are transported

to the cell membrane *(arrow 5)* where they can interact with neurotransmitters *(arrow* 6). Neurotransmitters can bind to the receptor, as shown in Figure 1 — 10. In addition to causing second messenger systems to be triggered, as shown in Figure 1 — 10, the bound neurotransmitter may also reversibly cause the membrane to form a *pit (arrow* 7). This process takes the bound receptor out of circulation when the neuron wants to decrease the number of receptors available. This can be reversed or it can progress into **lysosomes** *(arrow* 8), where receptors are destroyed *(arrow* 9). This helps to remove old

receptors so that they can be replaced by new receptors coming from DNA in the cell nucleus.

postsynaptic target neuron in a profound and enduring manner. Since the postsynaptic DNA has to wait until molecular pony express messengers make their way from the postsynaptic receptors, often located on dendrites, to the postsynaptic neuron's nucleus (Fig. 1 — 11), it can take a while for neurotransmission to begin influencing the postsynaptic target neurons' biochemical processes (Fig. 1 — 13). The time it takes from receptor occupancy by neurotransmitter to gene expression is usually hours. Furthermore, since the last messenger triggered by neurotransmission, called a transcription factor, only initiates the very beginning of gene action (Fig. 1 — 11), it takes even longer for the gene activation to be fully implemented via the series of biochemical events it triggers (Figs. 1 — 12 and 1 — 13). These biochemical events can begin many hours to days after the neurotransmission occurred and can last days or weeks once they are put in motion (Fig. 1 —13).

Thus, a brief puff of chemical neurotransmission from a presynaptic neuron can trigger a profound postsynaptic reaction, which takes hours to days to develop and can last days to weeks or even longer. Every conceivable component of this entire process of chemical neurotransmission is a candidate for modification by drugs. Most psychotropic drugs act on the processes that control chemical neurotransmission at the level of the neurotransmitters themselves or of their enzymes and especially their receptors. Future psychotropic drugs will undoubtedly act directly on the biochemical cascades, particularly on those elements that control the expression of pre- and postsynaptic genes. Also, mental and neurological illnesses are known or suspected to affect these same aspects of chemical neurotransmission.

Multiple Neurotransmitters

The known or suspected neurotransmitters in the brain already number several dozen (Table 1 — 1). Based on theoretical considerations of the amount of genetic material in neurons, there may be several hundred to several thousand unique brain chemicals. Originally, about half a dozen "classical" neurotransmitters were known. In recent years, an ever increasing number of neurotransmitters are being discovered. The classical neurotransmitters are relatively low molecular weight amines or amino acids. Now we know that strings of amino acids called *peptides* can also have neurotransmitter actions, and many of the newly discovered neurotransmitters are peptides, which are specifically called *neuropeptides* (Fig. 1—9).

God's Pharmacopoeia

Some naturally occurring neurotransmitters may be similar to drugs we use. For example, it is well known that the brain makes its own morphine (i.e., beta endorphin), and its own marijuana (i.e., anandamide). The brain may even make its own antidepressants, it own anxiolytics, and its own hallucinogens. Drugs often mimic the brain's natural neurotransmitters. Often, drugs are discovered prior to the natural neurotransmitter. Thus, we knew about morphine before the discovery of beta-endorphin; marijuana before the discovery of cannabinoid receptors and anandamide; the benzodiazepines diazepam (Valium) and alprazolam (Xanax) before the discovery of benzodiazepine receptors; and the antidepressants amitriptyline (Elavil) and fluoxetine (Prozac) before the discovery of the serotonin transporter site. This un-

Table 1 — 1. *Neurotransmitters in brain*

Amines
- Serotonin (5HT)
- Dopamine (DA)
- Norepinephrine (NE)
- Epinephrine (E)
- Acetylcholine (Ach)
- Tyramine
- Octopamine
- Phenylethylamine
- Tryptamine
- Melatonin
- Histamine

Pituitary Peptides
- Corticotropin (ACTH)
- Growth hormone (GH)
- Lipotropin
- Alpha-melanocyte—stimulating hormone (alpha-MSH)
- Oxytocin
- Vasoporessin
- Thyroid-stimulating hormone (TSH)
- Prolactin

Circulating Hormones
- Angiotensin
- Calcitonin Glucagon
- Insulin Leptin
- Atrial natriuretic factor
- Estrogens Androgens
- Progestins Thyroid hormones

Hypothalamic-Releasing Hormones
- Corticotropin-releasing factor (CRH)
- Gonadotropin-releasing hormone (GnRH)
- Somatostatin
- Thyrotropin-releasing hormone (TRH)

Amino Acids
- Gamma-aminobutyric acid (GABA)
- Glycine
- Glutamic acid (glutamate)
- Aspartic acid (aspartate)
- Gamma-hydroxybutyrate

Gut Hormones
- Cholecystokinin (CCK)
- Gastrin
- Motilin
- Pancreatic polypeptide
- Secretin
- Vasoactive intestinal peptide (VIP)

Opioid Peptides
- Dynorphin Beta-endorphin Met-enkephalin Leu-enkephalin
- Kyotorphin

Miscellaneous Peptides
- Bombesin
- Bradykinin
- Carnosine
- Neuropeptide Y
- Neurotensin Delta sleep factor
- Galanin Oxerin

Gases
- Nitric oxide (NO)
- Carbon monoxide (CO)

Lipid Neurotransmitter
- Anandamide

NeurokininslTachykinins
- Substance P
- Neurokinin A
- Neurokinin B

derscores the point made above that the great majority of drugs that act in the CNS act on the process of neurotransmission. Indeed, this apparently occurs at times in a manner that often replicates or mimics the actions of the brain itself when the brain uses its own chemicals.

Co-transmitters

Each neuron was originally thought to use one neurotransmitter only and to use it at all of its synapses. Today, we now know, however, that many neurons have more than one neurotransmitter (Table 1—2). Thus, the concept of co-transmission has arisen. This often involves a monoamine coupled with a neuropeptide. Under some conditions, the monoamine is released alone; under other conditions, both are released, adding to the repertoire of options for chemical neurotransmission by neurons that contain both neurotransmitters.

Incredibly, the neuron thus uses a certain "polypharmacy" of its own. The rationale behind the use and action of many drugs, however, grew up in the era of thinking about one neuron using only one neurotransmitter, so that the more selective a drug, perhaps the better it could modify neurotransmission. This may be true only to a point. That is, the physiological function of many neurons is now known to be that of communicating by using more than one neurotransmitter.

To replace or influence abnormal neurotransmission, it may therefore be necessary to use multiple drug actions. If the neuron itself uses polypharmacy, perhaps occasionally so should the psychopharmacologist. Today we still lack a rationale for specific multiple drug uses based on the principle of co-transmission, and so much polypharmacy is empirical or even irrational. As understanding of co-transmission increases, the scientific basis for multiple drug actions may well become established for clinical applications. In fact, this may explain why drugs with multiple mechanisms or multiple drugs in combination are the therapeutic rule rather than the exception in psychopharmacology practice. The trick is to be able to do this rationally.

Table 1 — 2. *Co-transmitter pairs*

Amine/Amino Acid	*Peptide*
Dopamine	Enkephalin
Dopamine	Cholecystokinin
Norepinephrine	Somatostatin
Norepinephrine	Enkephalin
Norepinephrine	Neurotensin
Epinephrine	Enkephalin
Serotonin	Substance P
Serotonin	Thyrotropin-releasing hormone
Serotonin	Enkephalin
Acetylcholine	Vasoactive intestinal peptide
Acetylcholine	Enkephalin
Acetylcholine	Neurotensin
Acetylcholine	Luteinizing-hormone-releasing hormone
Acetylcholine	Somatostatin
Gamma aminobutyric acid (GABA)	Somatostatin
Gamma aminobutyric acid (GABA)	Motilin

Molecular Neurobiology

As mentioned earlier, the purpose of chemical neurotransmission is to alter the function of postsynaptic target neurons. To understand the long-term consequences of chemical neurotransmission on the postsynaptic neuron (e.g., Fig. 1 — 13), it is necessary to understand the molecular mechanisms by which neurotransmission regulates gene expression. It is estimated that the human genome contains approximately 80,000 to 100,000 genes located within 3 million base pairs of DNA on 23 chromosomes. Incredibly, however, genes only occupy about 3% of all this DNA. The other 97% of DNA is not well understood, but it is obviously there for some reason. We may need to await the completion of the *Human Genome Project*, which hopes to sequence the entire 3 million base pairs within a few years, before the function of all this DNA is clarified. Once the DNA is sequenced, it will be easier to figure out what it does.

The general function of the various gene elements within the brain's DNA is well known; namely, they contain all the information necessary to synthesize the proteins that build the structures that mediate the specialized functions of neurons. Thus, if chemical neurotransmission ultimately activates the appropriate genes, all sorts of changes can occur in the postsynaptic cell. Such changes include making, strengthening, or destroying synapses; urging axons to sprout; and synthesizing various proteins, enzymes, and receptors that regulate neurotransmission in the target cell.

How does chemical neurotransmission regulate gene expression? We have already discussed how chemical neurotransmission converts receptor occupancy by a neurotransmitter into the creation of a second messenger (Fig. 1 — 10), followed by activation of enzymes, which in turn form transcription factors that turn on genes (Fig. 1 — 11). Most genes have two regions, a *coding* region and a *regulatory* region (Fig. 1 — 14). The coding region is the direct template for making its corresponding RNA. This DNA can be transcribed into its RNA with the help of an enzyme called *RNA polymerase*. However, RNA polymerase must be activated, or it will not function.

Luckily, the regulatory region of the gene can make this happen. It has an *enhancer element* and a *promoter element* (Fig. 1 — 14), which can initiate gene expression with the help of transcription factors. Transcription factors themselves can be activated when they are phosphorylated, which allows them to bind to the regulatory region of the gene (Fig. 1 — 15). This in turn activates RNA polymerase, and off we go with the coding part of the gene *transcribing* itself into its mRNA (Fig. 1 — 16). Once transcribed, of course, the RNA goes on to *translate* itself into the corresponding protein (Fig. 1 — 16).

If such changes in genetic expression lead to changes in connections and in the functions that these connections perform, it is easy to understand how genes can *modify behavior*. The details of nerve functioning, and thus the behavior derived from this nerve functioning, are controlled by genes and the products they produce. Since mental processes and the behavior they cause come from the connections between neurons in the brain, genes therefore exert significant control over behavior. But can behavior modify genes? Learning as well as experiences from the environment can indeed alter which genes are expressed and thus can give rise to changes in neuronal connections. In this way, human experiences, education, and even psychotherapy may change the expression of genes that alter the distribution and "strength" of specific synaptic connections. This, in turn, may produce long-term changes in behavior

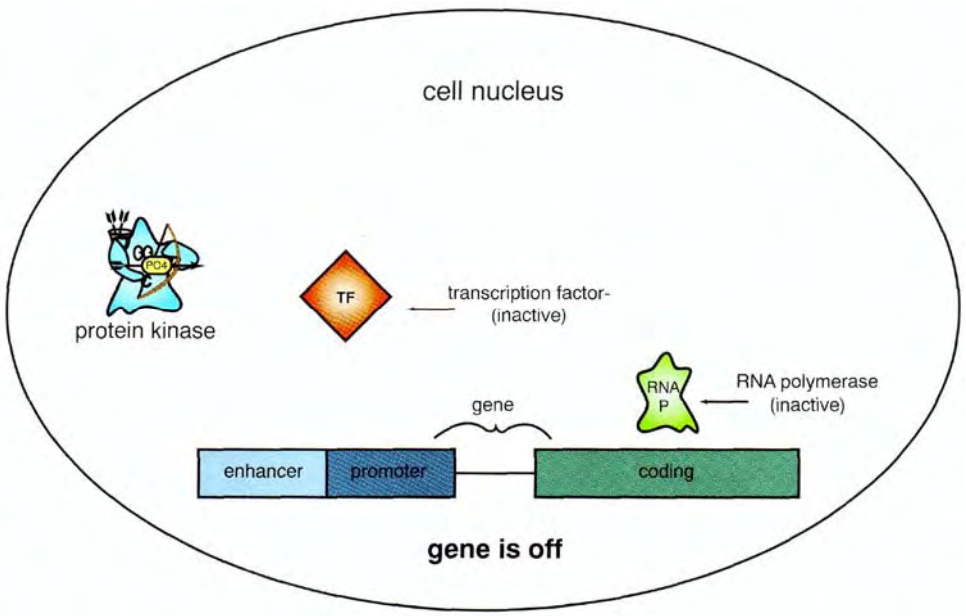

FIGURE 1 —14. Activation of a gene, part 1. Here the **gene is "off."** The elements of gene activation include the enzyme **protein kinase**, a **transcription factor**, the enzyme **RNA polymerase**, and the gene itself. This gene is off because the transcription factor has not yet been activated. The gene contains both a **regulatory region** and a **coding region**. The regulatory region has both an **enhancer element** and a **promoter element**, which can initiate gene expression when they interact with activated transcription factors. The coding region is directly transcribed into its corresponding RNA once the gene is activated.

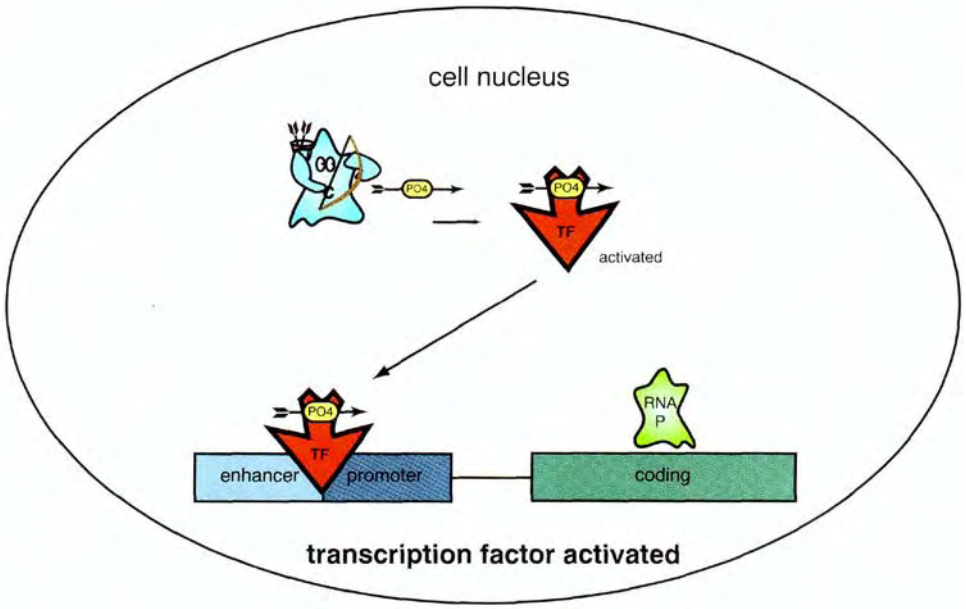

FIGURE 1-15. Activation of a gene, part 2. The **transcription factor** is now **activated** because it has been phosphorylated by protein kinase allowing it to bind to the regulatory region of the gene.

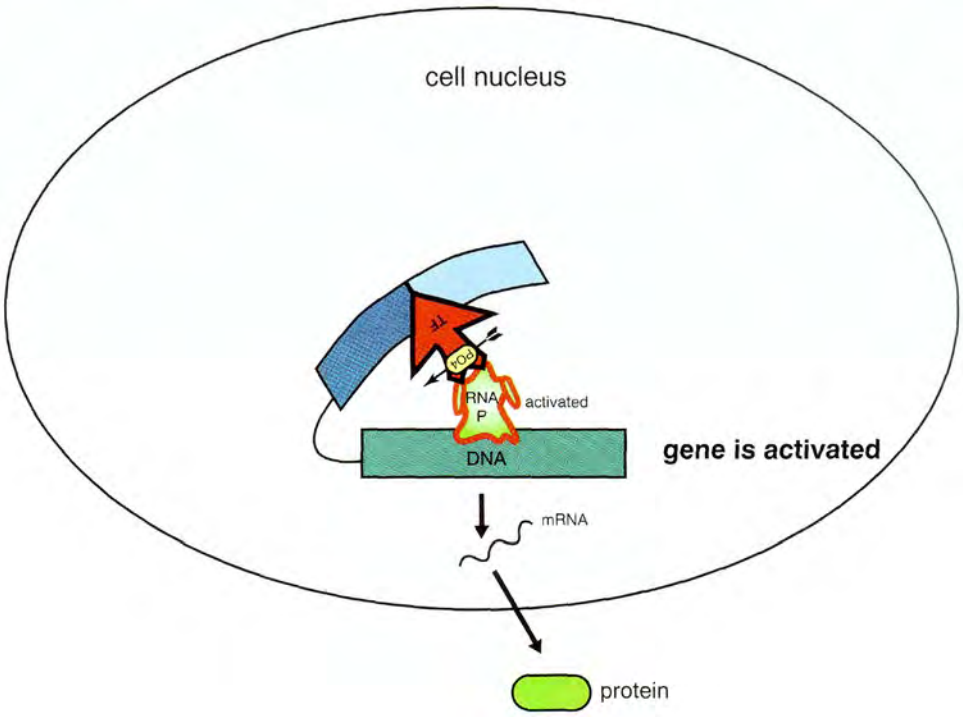

FIGURE 1 — 16. Activation of a gene, part 3. The **gene** itself is now **activated** because the transcription factor has bound to the regulatory region of the gene, activating in turn the enzyme RNA polymerase. Thus, the gene is transcribed into mRNA, which in turn is translated into its corresponding protein. This protein is thus the product of activation of this particular gene.

caused by the original experience and mediated by the genetic changes triggered by that original experience. Thus, genes modify behavior and behavior modifies genes.

Enzymes (Fig. 1—7) and receptors (Fig. 1—8) are specific examples of proteins encoded within the neuron's genes and synthesized when the appropriate gene is turned on (see also Fig. 1 — 12). A complete understanding of receptor function involves knowing the exact structure of the receptor protein, based on its amino acid sequence. This can be derived from cloning the receptor by standard molecular techniques. Subtle differences in receptor structure can be the key to explaining distinctions between receptors in various species (e.g., humans versus experimental animals), in certain diseases (i.e., "sick" versus healthy receptors), and in pharmacological subtypes of receptors (i.e., receptors that bind the same neurotransmitters but do so quite differently and with vastly different pharmacologic properties). This will be amplified in Chapter 2.

Molecular neurobiology techniques thus help to clarify receptor functioning in neurotransmission by giving scientists the structure of the receptor. Knowledge of receptor structure also assists in refining receptors as targets for chemists trying to develop new drugs. Knowing the structure of receptors especially allows comparisons of receptor families of similar structure and may ultimately lead to describing changes in receptor structure caused by inherited disease and by drug administration.

Although receptors are usually discovered after neurotransmitters and drugs are found to bind to them, sometimes it happens the other way around. That is, if the

gene for a receptor with no known ligand is characterized, it is known as an "orphan receptor," waiting to be adopted by a ligand to be discovered in the future.

The conceptual point to grasp here is that the genome (i.e., DNA) is responsible for the production of receptors, and the production of receptors can be modulated by physiological adaptations, by drugs, and by diseases.

Neurodevelopment and Neuronal Plasticity

Understanding of human brain development is advancing at a rapid pace. Most neurons are formed by the end of the second trimester of prenatal life (Fig. 1 — 17). Neuronal migration starts within weeks of conception and is largely complete by birth. Thus, human brain development is more dynamic before birth than during adulthood, and brain volume is 95% of its adult size by age 5. On the other hand, several processes affecting brain structure persist throughout life. Myelination of axon fibers and branching, or arborization, of neurons into their tree-like structures continue at least throughout adolescence. Synaptogenesis seemingly occurs throughout a lifetime.

Thus, both the neuron and its synapses are quite "plastic," changeable, and malleable. Surprising recent reports suggest that some neurons can divide after birth, even in mature mammalian brains and possibly even in human brains. Equally shocking, however, is the discovery that periodically throughout the life cycle and under certain conditions neurons kill themselves in a type of molecular hari-kari called *apoptosis.* In fact, up to 90% of the neurons that the brain makes during fetal development commit apoptotic suicide before birth. Since the mature human brain contains approximately 100 billion neurons, perhaps nearly 1 trillion are initially formed and hundreds of billions apoptotically destroyed between conception and birth.

How do neurons kill themselves? Apoptosis is programmed into the genome of various cells including neurons, and when activated, causes the cell to self-destruct. This is not the messy affair associated with cellular poisoning or suffocation known as necrosis (Fig. 1 — 18). Necrotic cell death is characterized by a severe and sudden injury associated with an inflammatory response. By contrast, apoptosis is more subtle, akin to fading away. Apoptotic cells shrink, whereas necrotic cells explode (Fig. 1 — 18). The original scientists who discovered apoptosis coined that term to rhyme with necrosis, and also to mean literally a "falling off," as the petals fall off a flower or the leaves fall from a tree. The machinery of cell death is a set of genes that stand ever ready to self-destruct if activated.

Why should a neuron "slit its own throat" and commit cellular suicide? For one thing, if a neuron or its DNA is damaged by a virus or a toxin, apoptosis destroys and silently removes these sick genes, which may serve to protect surrounding healthy neurons. More importantly, apoptosis appears to be a natural part of development of the immature CNS. One of the many wonders of the brain is the built-in redundancy of neurons early in development. These neurons compete vigorously to migrate, innervate target neurons, and drink trophic factors necessary to fuel this process. Apparently, there is survival of the fittest, because 50 to 90% of many types of neurons normally die at this time of brain maturation. Apoptosis is a natural mechanism to eliminate the unwanted neurons without making as big a molecular mess as necrosis would.

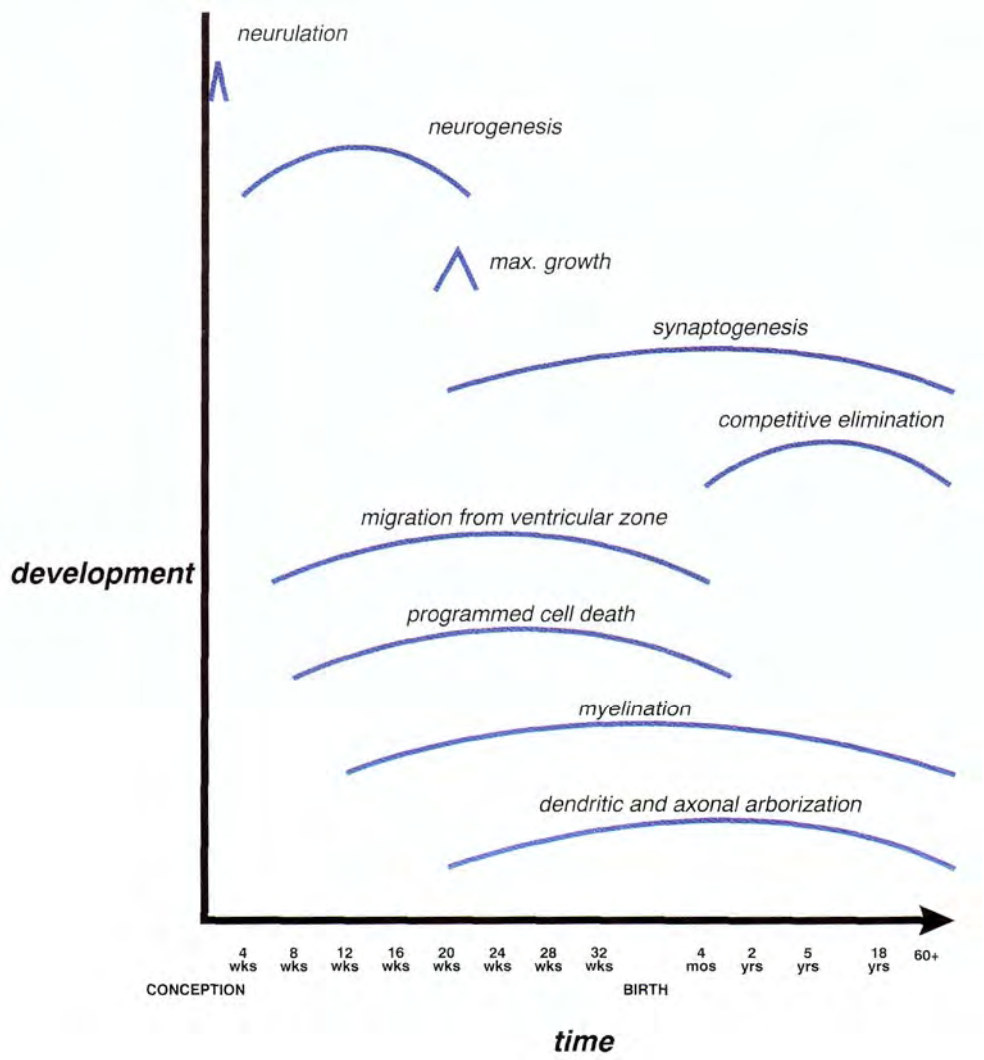

FIGURE 1 — 17. Time course of brain development. The earliest events of neuronal and brain development in humans are shown at the top, with subsequent and longer-lasting events shown in the lower panels. **Maximum growth** of new neurons is complete before birth, as are the processes of **neuronal migration** and **programmed cell death.** After birth, **synaptogenesis, myelination,** and **dendritic and axonal arborization** occur throughout the individual's lifetime. **Competitive elimination** of synapses, not neurons, is at its peak around pubescence.

Dozens of neurotrophic factors regulate the survival of neurons in the central and peripheral nervous systems (Table 1 — 3). A veritable alphabet soup of neurotrophic factors contributes to the brain broth of chemicals that bathe and nourish nerve cells. Some are related to nerve growth factor (NGF), others to glial cell line—derived neurotrophic factor (GDNF) and still others to various other neurotrophic factors (Table 1 — 3). Some neurotrophic factors can trigger neurons to commit cellular suicide by making them fall on their apoptotic swords. The brain seems to choose which nerves live or die partially by whether a neurotrophic factor nourishes them

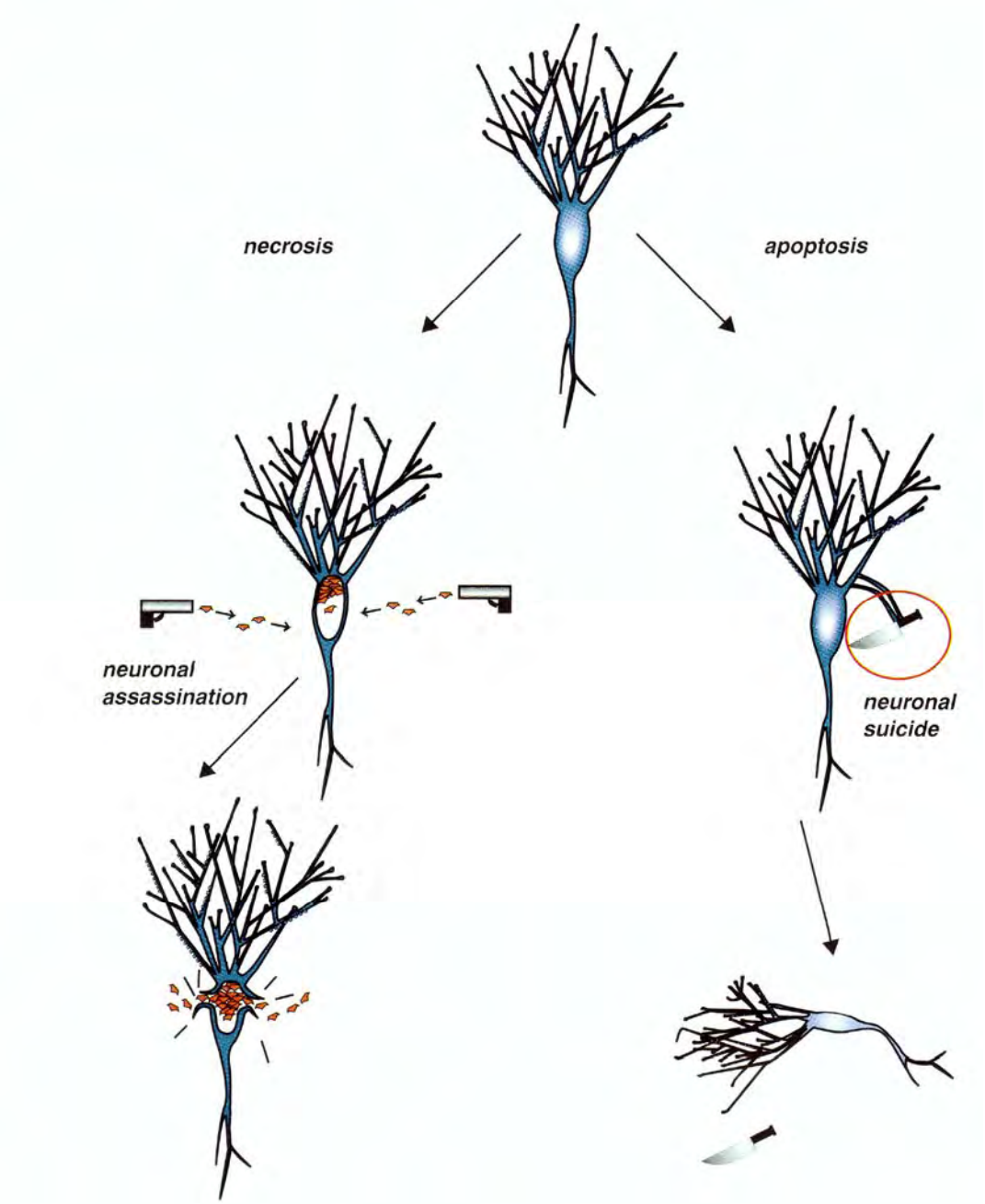

FIGURE 1 — 18. Neuronal death can occur by either **necrosis** or **apoptosis.** Necrosis is analogous to neuronal assassination, in which neurons explode and cause an inflammatory reaction after being destroyed by poisons, suffocation, or toxins such as glutamate. On the other hand, apoptosis is akin to neuronal suicide and results when the genetic machinery is activated to cause the neuron to literally "fade away" without causing the molecular mess of necrosis.

Table 1 — 3. *Neurotrophin factors: An alphabet soup of brain tonics*

NGF	Nerve growth factor
P75	Proaptotic receptors
TrkA	Antiaptotic receptors
GDNF	Glial cell line—derived neurotrophic factors including neurturin, c-REF, and R-alpha
BDNF	Brain-derived neurotrophic factor
NT-3, 4 and 5	Neurotrophins 3, 4, and 5
CNTF	Ciliary neurotrophic factr
ILGF I and II	Insulin-like growth factors
FGF	Fibroblast growth factor (comes in both acidic and basic forms)
EGF	Epidermal growth factor

Table 1—4. *Recognition molecules*

PSA-NCAM, polysialic acid—neuronal cell adhesion molecule
NCAM, neuronal cell adhesion molecules (such as H-CAM, G-CAM, VCAM-1)
APP, amyloid precursor protein
Integrin
N-Cadherin
Laminin
Tenscin
Proteoglycans
Heparin-binding growth-associated molecule
Glial hyaluronate—binding protein
Clusterin

or chokes them to death. That is, certain molecules (such as NGF) can interact at proapoptotic "grim reaper" receptors to trigger apoptotic neuronal demise. However, if NGF decides to act on a neuroprotective "bodyguard" receptor, the neuron prospers.

Not only must the correct neurons be selected, but they must migrate to the right parts of the brain. While the brain is still under construction in utero, whole neurons wander. Later, only their axons can move. Neurons are initially produced in the center of the developing brain. Consider that 100 billion human neurons, selected from nearly 1 trillion, must migrate to the right places in order to function properly. What could possibly direct all this neuronal traffic? It turns out that an amazing form of chemical communication calls the neurons forth to the right places and in the right sequences. At speeds up to 60 millionths of a meter per hour, they travel to their proper destination, set up shop, and then send out their axons to connect with other neurons.

These neurons know where to go because of a series of remarkable chemical signals, different from neurotransmitters, called *adhesion molecules* (Table 1—4). First, glial cells form a cellular matrix. Neurons can trace glial fibers like a trail through the brain to their destinations. Later, neurons can follow the axons of other neurons

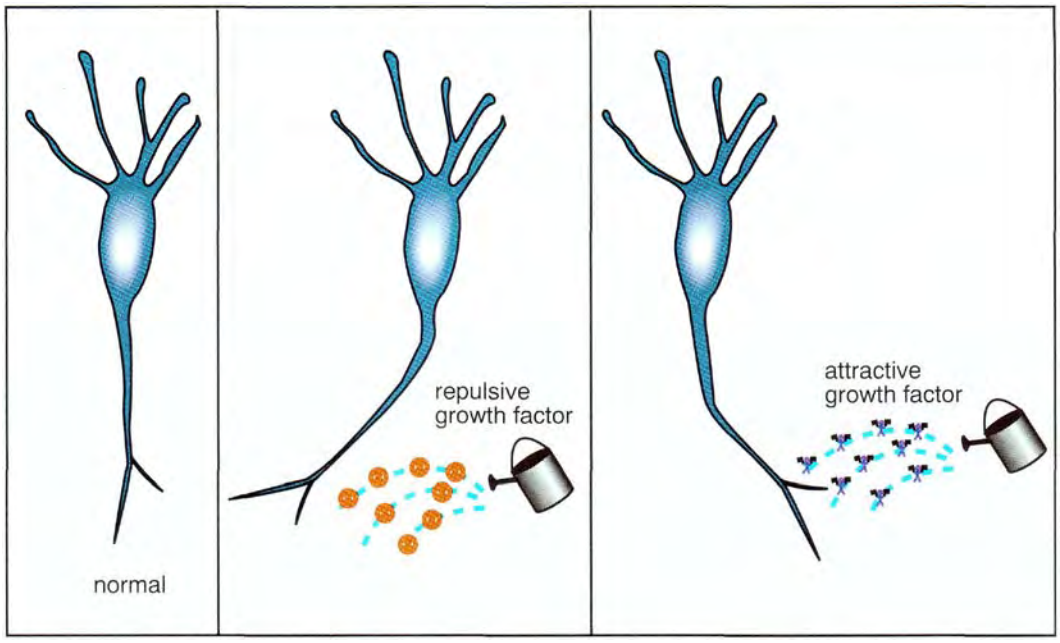

FIGURE 1 —19. Neurotrophic factors can be **repulsive** *{middle panel)* and cause axons to grow away from such molecules. Neurotrophic factors can also be **attractant** and encourage axonal growth toward such molecules. Neurotrophic factors thus direct axonal traffic in the brain and help determine which axons synapse with which postsynaptic targets.

already in place and trace along the trail already blazed by the first neuron. Adhesion molecules are coated on neuronal surfaces of the migrating neuron, and complementary molecules on the surface of glia allow the migrating neuron to stick there. This forms a kind of molecular Velcro, which anchors the neuron temporarily and directs its walk along the route paved by the appropriate cell surfaces. Settlement of the brain by migrating neurons is complete by birth, but axons of neurons can grow for a lifetime on activation.

Once neurons settle down in their homesteads, their task is to form synapses. How do their axons know where to go? Neurotrophins not only regulate which. neuron lives or dies, but also whether an axon sprouts and which target it innervates. During development in the immature brain, neurotrophins can cause axons to cruise all over the brain, following long and complex pathways to reach their correct targets. Neurotrophins can induce neurons to sprout axons by having them form an axonal growth cone. Once the growth cone is formed, neurotrophins as well as other factors make various recognition molecules for the sprouting axon, presumably by having neurons and glia secrete these molecules into the chemical stew of the brain's extracellular space.

These recognition molecules can either repel or attract growing axons, sending directions for axonal travel like a semaphore signaling a navy ship (Fig. 1 —19). Indeed, some of these molecules are called semaphorins to reflect this function. Once the axon growth tip reaches port, it is told to collapse by semaphorin molecules called collapsins, allowing the axon to dock into its appropriate postsynaptic slip

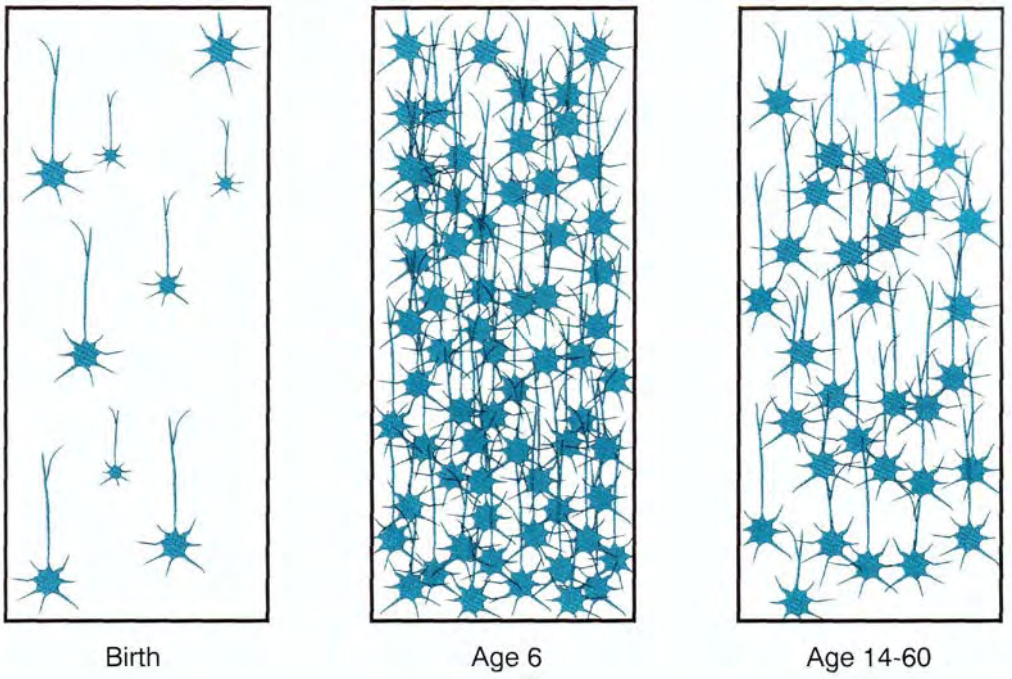

FIGURE 1—20. Synapses are formed at a furious rate between birth and age 6. However, there is competitive elimination and restructuring of synapses, a phenomenon that peaks during pubescence and adolescence, leaving about half to two-thirds of the synapses present in childhood to survive into adulthood.

and not sail past it. Other recognition molecules direct axons away by emitting repulsive axon guidance signals (RAGS) (Fig. 1 — 19).

As brain development progresses, the travel of axonal growth cones is greatly impeded but not completely lost. The fact that axonal growth is retained in the mature brain suggests that neurons continue to alter their targets of communication, perhaps by repairing, regenerating, and reconstructing synapses as demanded by the evolving duties of a neuron. A large number of recognition molecules supervise this. Some of these include not only semaphorins and collapsins but also molecules such as netrins, neuronal cellular adhesion molecules (NCAMS), integrins, cadherins, and cytokines (Table 1—4).

Interestingly, more synapses are present in the brain by age 6 than at any other time in the life cycle (Fig. 1 — 20). During the next 5 to 10 years and into adolescence, the brain then systematically removes half of all synaptic connections present at age 6. This leaves about 100 trillion synapses and up to 10,000 individual synapses for some neurons. Excitotoxicity may mediate the pruning of synaptic connections (as will be discussed in much greater detail in Chapter 4). Hopefully, neu-rodevelopmental experiences and genetic programming lead the brain to select wisely which connections to keep and which to destroy. If this is done appropriately, the individual prospers during this maturational task and advances gracefully into adulthood. Bad selections theoretically could lead to neurodevelopmental disorders such as schizophrenia or even attention deficit hyperactivity disorder.

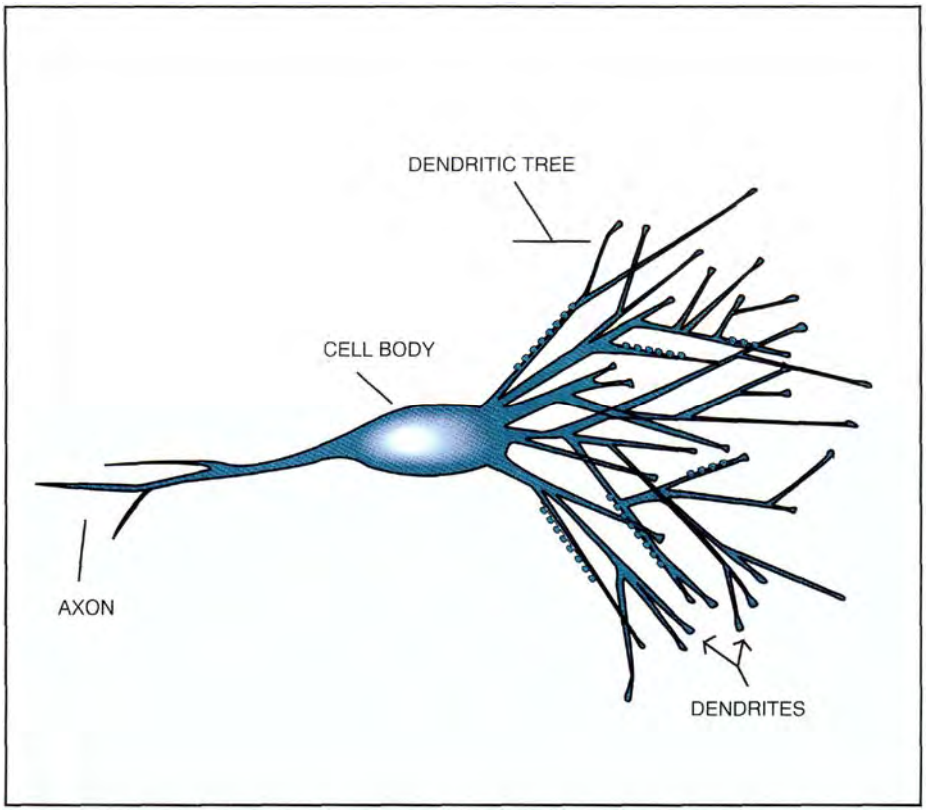

FIGURE 1—21. The neuron is composed of a **cell body**, an **axon** and a **dendritic tree** (literally, a tree of branching dendrites). The dendritic tree is in constant flux and revises its synaptic connections throughout life.

That growth of new synapses and the pruning of old synapses then proceeds throughout a lifetime, but at a much slower pace and over shorter distances than earlier in development. Thus, the axons and dendrites of each neuron are constantly changing, establishing new connections, and removing old connections, in a manner reminiscent of the branches of a tree (Fig. 1—21). Indeed, the *arborization* of neuronal terminals and the *dendritic tree* are terms implying this constant branching (Fig. 1 — 22) and pruning (Fig. 1—23) process, which proceeds throughout the lifetime of that neuron. After the dramatic reductions in neurons before birth and in synapses during late childhood and early adolescence are complete, activity calms down considerably in the mature brain, where maintenance and remodeling of synapses continue to modest extents and over more limited distances.

Although the continuous structural remodeling of synapses in the mature brain, directed by recognition molecules, cannot approximate the pronounced long-range growth of early brain development, this restriction could be beneficial, in part because it allows structural plasticity while restricting unwanted axonal growth. This would stabilize brain function in the adult and could furthermore prevent chaotic rewiring of the brain by limiting both axonal growth away from appropriate targets and ingrowth from inappropriate neurons. On the other hand, the price of such

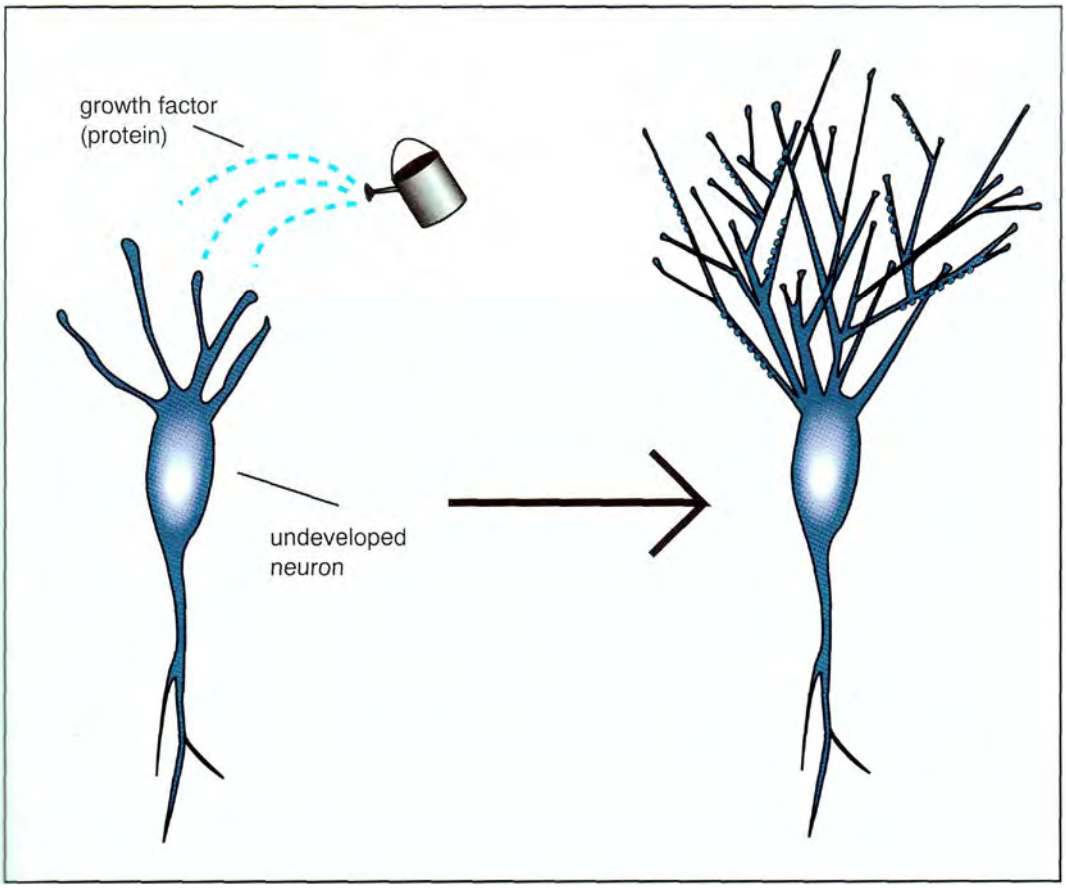

FIGURE 1 — 22. The dendritic tree of a neuron can sprout branches, grow, and establish a multitude of new synaptic connections throughout its life. The process of making dendritic connections on an **undeveloped neuron** may be controlled by various **growth factors**, which act to promote the branching process and thus the formation of synapses on the dendritic tree.

growth specificity becomes apparent when a long-distance neuron in the adult brain or spinal cord dies, thus making it difficult to reestablish original synaptic connections, even if axonal growth is turned on.

As previously discussed, neurons and their supportive and neighboring glia elaborate a rich array of neurotrophic factors, which promote synaptic connections (Fig. 1—22) or eliminate them (Fig. 1—23). The potential for releasing growth factors is preserved forever, which contributes to the possibility of constant synaptic revision throughout the lifetime of that neuron. Such potential changes in synaptogenesis may provide the substrate for learning, emotional maturity, and the development of cognitive and motor skills throughout a lifetime. However, it is not clear how the brain dispenses its neurotrophic factors endogenously during normal adult physiological functioning. Presumably, demand to use neurons is met by keeping them fit and ready to function, a task accomplished by salting the brain broth with neurotrophic factors that keep the neurons healthy. Perhaps thinking and learning provoke the release of neurotrophic factors. Maybe "use it or lose it" applies to adult neurons.

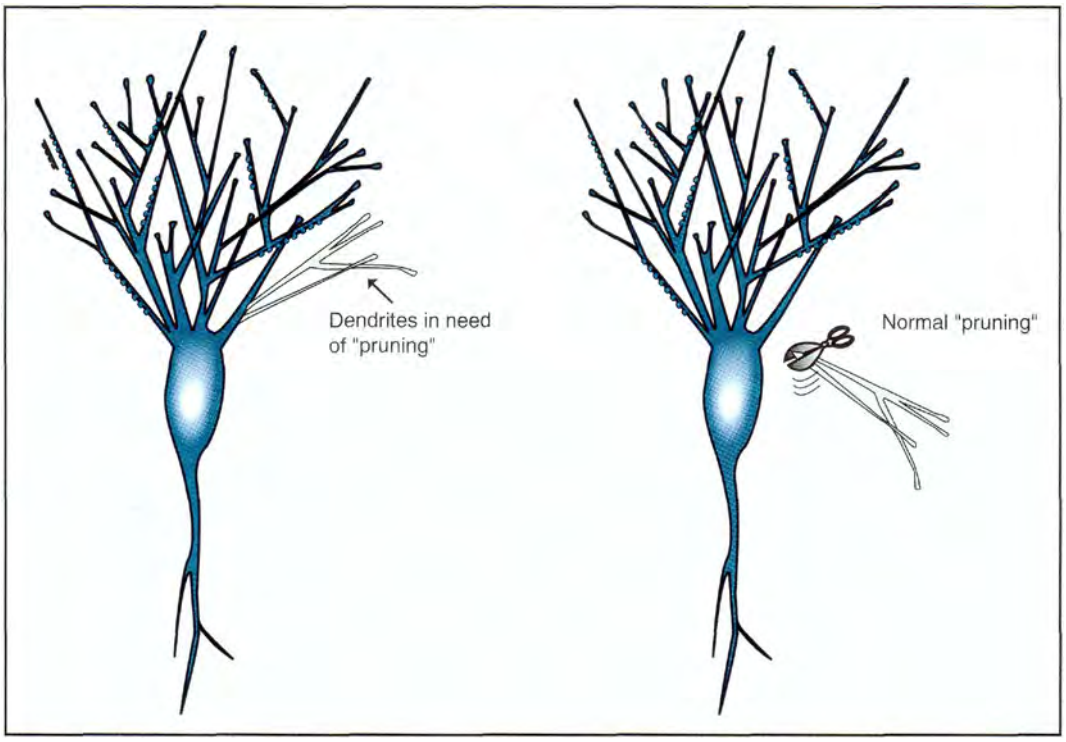

FIGURE 1—23. The dendritic tree of a neuron not only sprouts branches, grows, and establishes a multitude of new synaptic connections throughout its life, as shown in Figure 1—22, but it can also remove, alter, trim, or destroy such connections when necessary. The process of dismantling synapses and dendrites may be controlled by removal of growth factors or by a naturally occurring destructive process sometimes called *excitotoxicity.* Thus, there is a **normal "pruning"** process for removing **dendrites in need of pruning.**

with neurons being preserved and new connections being formed if the brain stays active. It is even possible that the brain could lose its "strength" in the absence of mental exercise. Perhaps inactivity leads to pruning of unused, "rusty" synapses, even triggering apoptotic demise of entire inactive neurons. On the other hand, mental stimulation might prevent this, and psychotherapy may even induce neurotrophic factors to preserve critical cells and innervate new therapeutic targets to alter emotions and behaviors. Only future research will clarify how to use drugs and psychotherapy to balance the seasonings in the tender stew of the brain.

Summary

The reader should now appreciate that chemical neurotransmission is the foundation of psychopharmacology. It has three dimensions, namely, space, time, and function. The *spatial* dimension is both that of "hard wiring" as the anatomically addressed nervous system and that of a "chemical soup" as the chemically addressed nervous system. The *time* dimension reveals that neurotransmission can be fast (milliseconds) or slow (up to several seconds) in onset, depending on the neurotransmitter or neuromodulator, of which there are dozens. Neurotransmission can also cause actions

that are short-acting (milliseconds) or very long acting (days to weeks or longer). The *functional* dimension of chemical neurotransmission is the process whereby an electrical impulse in one neuron is converted into a chemical message at the synaptic connection between two neurons and then into a chemical message that can alter gene expression in the second neuron.

This chapter has also emphasized a few additional points: Chemical neurotransmission sometimes occurs with more than one neurotransmitter in a single neuron. Naturally occurring neurotransmitters are often mimicked by drugs (for example, marijuana and morphine). Molecular neurobiology and its techniques demonstrate that the genetic materials of a neuron are responsible for the production of neuronal proteins in general and neurotransmitter receptors in particular. This can be modulated by physiological adaptations, by drugs, and by diseases. Finally, the neuron is dynamically modifying its synaptic connections throughout its life, in response to learning, life experiences, genetic programming, drugs, and diseases.