

# NEUROTRANSMITTERS AND SIGNAL TRANSDUCTION

ERIC J. NESTLER  
AND RONALD S. DUMAN

---

Neuropsychopharmacology continues to be organized primarily according to the neurotransmitters that are utilized by various populations of neurons for synaptic transmission. This is because the vast majority of psychotropic drugs presently used clinically to treat neuropsychiatric disorders still have as their initial targets proteins that regulate the availability of a particular neurotransmitter (e.g., presynaptic reuptake transporters, synthetic or degradative enzymes) or that serve as ligands for particular neurotransmitter receptors. It is entirely appropriate then that this edition of *Neuropsychopharmacology: A Generation of Progress* begins with a section devoted to the major neurotransmitter systems in the brain. Rather than provide a comprehensive review of the now vast literature on neurotransmitter systems, the goal of this section is to highlight recent advances in the field.

Glutamate, as described in the chapter by Joseph Coyle, Michael Leski, and John Morrison, is the major excitatory neurotransmitter in the brain. During the past decade, numerous subtypes of glutamate transporters and glutamate receptors have been identified and characterized. Each of these represents a potentially exciting target for new pharmacotherapeutic agents. Richard Olsen focuses on  $\gamma$ -aminobutyric acid (GABA), which serves as the major inhibitory neurotransmitter in the brain. GABA receptors and GABA transporters are important targets for commonly used antianxiety, anticonvulsant, and antimanic medications. Agents with improved specificity toward subtypes of these proteins may offer substantial benefit as future treatments.

The next several chapters focus on other small-molecule neurotransmitters, which are used by relatively small fractions of neurons and generally serve to modulate the efficacy of glutamatergic and GABAergic synapses through diffuse projections throughout the neuraxis. Such neurotransmit-

ters include the catecholamines, norepinephrine, and dopamine. Norepinephrine, covered in a chapter by Gary Aston-Jones, regulates mood, attention, and alertness and is a substrate for many commonly used antidepressants. Dopamine, discussed in a chapter by Anthony Grace, plays a critical role in movement and reward. Accordingly, it is involved in movement disorders such as Parkinson's disease and is a common target for most drugs of abuse. The catecholamines, along with serotonin and histamine, are often referred to as *monoamine neurotransmitters* because they contain a single amine group. Serotonin is critically involved in many brain functions and is the target for many commonly used antidepressants. George Aghajanian and Elaine Sanders-Bush focus on new findings about serotonin, including the discovery and characterization of 14 distinct serotonin receptors and their physiologic functions. Histamine is discussed by Jean-Charles Schwartz and Jean-Michel Arrang. Although it has been known for some time that histamine regulates alertness and sleep, new advances in histamine pharmacology have been made possible by the cloning of three distinct histamine receptors. Finally, acetylcholine is often categorized along with the monoamines because it too is concentrated in discrete regions of the brain, many of which project diffusely to other parts of the brain. A major goal of neuropsychopharmacology research, as discussed by Marina Picciotto, Meenakshi Alreja, and J. David Jentsch, continues to be the development of drugs that are selective for the many subtypes of cholinergic receptors expressed in the central nervous system.

Many other types of molecules serve neurotransmitter functions. Michael Williams covers the so-called purinergic neurotransmitters, which include adenosine and adenosine triphosphate. The last few years have seen the cloning and characterization of a vast number of purinergic receptors,

with very different transmitter selectivities and functional properties. It is believed that selective ligands at these various receptors may serve as novel drugs in the treatment of Parkinson's disease, insomnia, anxiety, and pain, to name a few. Many types of polypeptides serve as neurotransmitters; these molecules are often termed *neuropeptides*. Significant recent progress has been made in understanding the physiologic role and pharmacology of certain neuropeptides, which are discussed in several chapters in this section. Gavan McNally and Huda Akil cover the opioid peptides, including a newly discovered opioid-like peptide, termed *orphanin-FQ* or *nociceptin*, that promotes nociception. Errol De Souza and Dimitri Grigoriadis review recent advances in the understanding of corticotropin-releasing factor, including the identification of two main types of receptors for corticotropin-releasing factor and other peptides (e.g., urocortin) that serve as endogenous ligands for the receptors. Nadia Rupniak and Mark Kramer focus on substance P and related neurokinins. Long known to be involved in the regulation of pain perception, recent evidence suggests that antagonists at certain neurokinin receptors may be effective antidepressants.

Despite the importance of neurotransmitter systems in neuropsychopharmacology, it must be emphasized that all the proteins that account for neurotransmitter synthesis and degradation, reuptake, and receptors, and for neuropeptide transmitters themselves, represent a small fraction of the perhaps hundreds of thousands of proteins expressed in the adult brain. A central promise of neuropsychopharmacology as we enter a new century is to evaluate these vast arrays of other proteins as targets for entirely new families of pharmacotherapeutic agents. Robert Malenka reviews what we

know about synaptic plasticity, the processes by which the efficacy of transmission at particular synapses is altered as a consequence of synaptic activity. Mark von Zastrow covers the molecular and cellular mechanisms underlying receptor internalization, a process in which the numbers of many and perhaps most types of neurotransmitter receptors on the plasma membrane are regulated by synaptic activity. David Russell and Ronald Duman offer an overview of neurotrophic factors and their signaling pathways. Neurotrophic factors have long been recognized for their role in neural growth and differentiation during development, and we now know they are also important for regulating the survival and plasticity of adult neurons. Eric Nestler and Steven Hyman review the intracellular signaling pathways by which neurotransmitters, acting on plasma membrane receptors, regulate gene expression. Such regulation represents a prominent mechanism of long-term plasticity in the nervous system, including the actions of repeated exposure to psychotropic drugs (e.g., antidepressant action and drug addiction). Pierre Magistretti and Bruce Ransom discuss the role of glial cells in the central nervous system—in particular, their control of the energy metabolism in the brain. Finally, Fred Gage and Henriette van Praag summarize new knowledge of neurogenesis in the adult brain. The recent discovery that new neurons are born in certain regions of the brain each day, and may be incorporated into the existing circuitry within those regions, raises new hope for the treatment of neurodegenerative and other neuropsychiatric disorders. The subject matter of these last several chapters has not yet been exploited pharmacologically, but it is believed that the next generation of progress will see new pharmacologic agents directed at these nontraditional mechanisms.