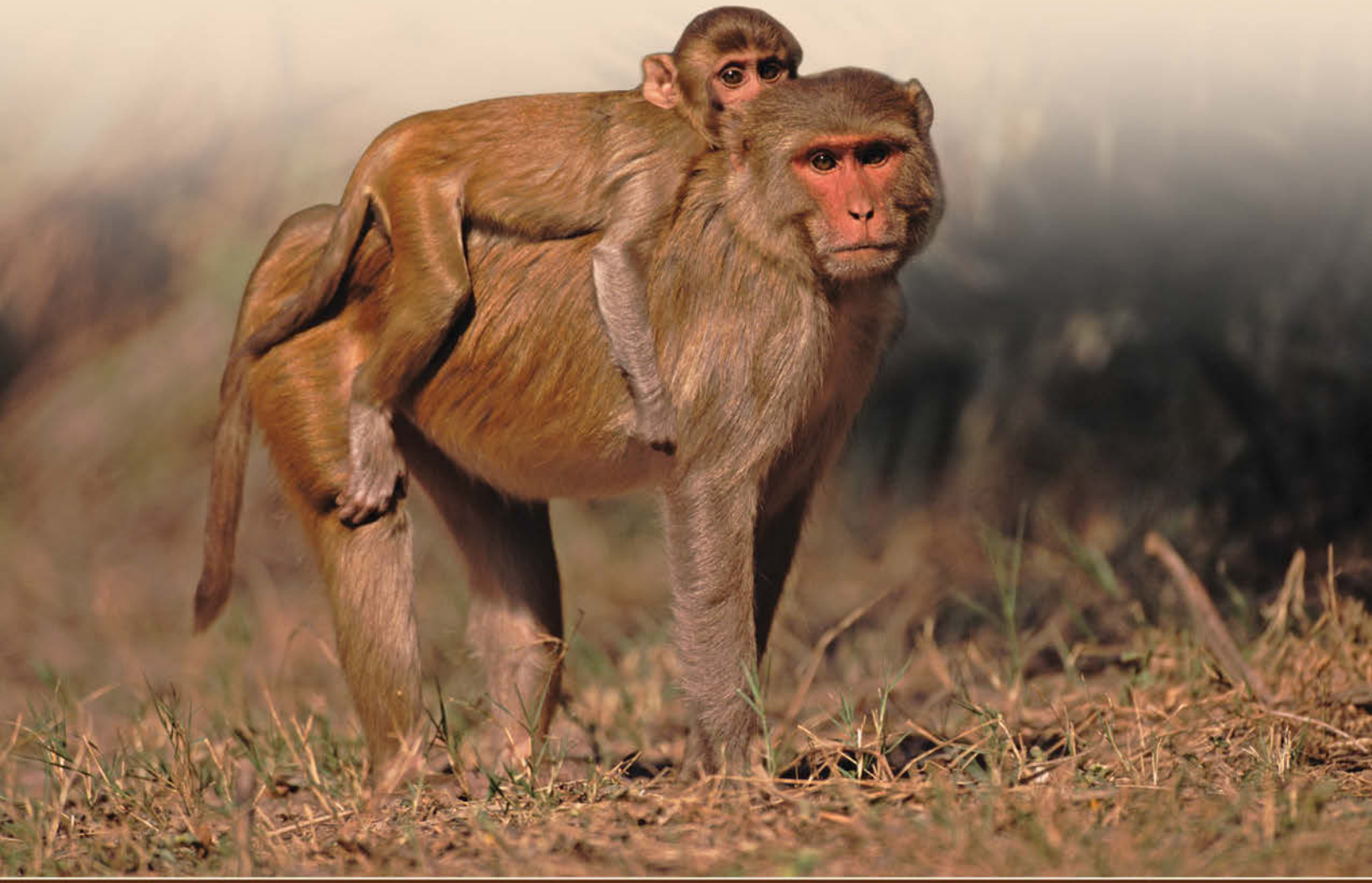
An Introduction to Behavioral Endocrinology

Fifth Edition



Randy J. Nelson • Lance J. Kriegsfeld

VERTEBRATE STEROID HORMONES

Hormone	Abbreviation	Source	Major biological action
Adrenal glands			
MINERALOCORTICOIDS			
Aldosterone		Zona glomerulosa of adrenal cortex	Sodium retention in kidney
11-Deoxycorticosterone	DOC	Zona glomerulosa of adrenal cortex	Sodium retention in kidney
GLUCOCORTICOIDS			
Cortisol (Hydrocortisone)	F	Zona fasciculata and z. reticularis of adrenal cortex	Increases carbohydrate metabolism; antistress hormone
Corticosterone	B	Zona fasciculata and z. reticularis of adrenal cortex	Increases carbohydrate metabolism; antistress hormone
Dehydroepiandrosterone	DHEA	Zona reticularis of adrenal cortex	Weak androgen; primary secretory product of fetal adrenal cortex
Ovaries			
Estradiol	E_2	Follicles	Uterine and other female tissue development
Estriol	E_3	Follicles, placenta	Uterine and mammary tissue development
Estrone	E_1	Follicles	Uterine and mammary tissue development
Progesterone	P_4	Corpora lutea, placenta	Uterine development; mammary gland development; maintenance of pregnancy
Testes			
Androstenedione		Leydig cells	Male sex characters
Dihydrotestosterone	DHT	Seminiferous tubules and prostate	Male secondary sex characters
Testosterone	T	Leydig cells	Spermatogenesis; male secondary sex characters

PEPTIDE AND PROTEIN HORMONES

Hormone	Abbreviation	Source	Major biological action
Adipose Tissue			
Leptin (Ob protein)		Adipocytes	Regulation of energy balance
Adiponectin		Adipocytes	Modulates endothelial adhesion molecules
Plasminogen activator inhibitor-1	PAI-1	Adipocytes	Regulation of vascular hemostasis
Adrenal glands			
Met-enkephalin		Adrenal medulla	Analgesic actions in CNS
Leu-enkephalin		Adrenal medulla	Analgesic actions in CNS
Gut			
Bombesin		Neurons and endocrine cells of gut	Hypothermic hormone; increases gastrin secretion
Cholecystokinin (Pancreozymin)	CCK	Duodenum and CNS	Stimulates gallbladder contraction and bile flow; affects memory, eating behavior
Gastric inhibitory polypeptide	GIP	Duodenum	Inhibits gastric acid secretion
Gastrin		G-cells of midpyloric glands in stomach antrum	Increases secretion of gastric acid and pepsin
Gastrin-releasing peptide	GRP	GI tract	Stimulates gastrin secretion
Ghrelin		Stomach mucosa/GI tract	Regulation of energy balance
Glucagon-like peptide-1	GLP-1	L cells of intestine	Regulates insulin secretion

PEPTIDE AND PROTEIN HORMONES (continued)

Hormone	Abbreviation	Source	Major biological action
Motilin		Duodenum, pineal gland	Alters motility of GI tract
Secretin		Duodenum	Stimulates pancreatic acinar cells to release bicarbonate and water
Vasoactive intestinal polypeptide	VIP	GI tract, hypothalamus	Increases secretion of water and electrolytes from pancreas and gut; acts as neurotransmitter in autonomic nervous system
Peptide YY	PYY	GI tract	Regulation of energy balance/food intake
Heart			
Atrial naturetic factor	ANF	Atrial myocytes	Regulation of urinary sodium excretion
Hypothalamus			
Agouti-related protein	AgRP	Arcuate nuclei	Regulation of energy balance
Arg-vasotocin	AVT	Hypothalamus and pineal gland	Regulates reproductive organs
Corticotropin-releasing hormone	CRH	Paraventricular nuclei, anterior periventricular nuclei	Stimulates release of ACTH and β-endorphin from anterior pituitary
Gonadotropin-releasing hormone (Luteinizing hormone–releasing hormone)	GnRH (LHRH)	Preoptic area; anterior hypothalamus; suprachiasmatic nuclei; medial basal hypothalamus (rodents and primates); arcuate nuclei (primates)	Stimulates release of FSH and LH from anterior pituitary
Gonadotropin-inhibitory hormone	GnIH	Species-dependent loci	Inhibits release of LH (in birds)
Kisspeptin		Species-dependent loci	Enhances GnRH release
Somatostatin (Growth hormone–inhibiting hormone)		Anterior periventricular nuclei	Inhibits release of GH and TSH from anterior pituitary, inhibits release of insulin and glucagons from pancreas
Somatocrinin (Growth hormone–releasing hormone)	GHRH	Medial basal hypothalamus; arcuate nuclei	Stimulates release of GH from anterior pituitary
Melanotropin-release inhibitory factor (Dopamine)	MIF (DA)	Arcuate nuclei	Inhibits the release of MSH (no evidence of this peptide in humans)
Melanotropin-releasing hormone	MRH	Paraventricular nuclei	Stimulates the release of MSH from anterior pituitary (no evidence of this peptide in humans)
Melanin-concentrating hormone	MCH	Lateral hypothalamus	Increases food intake
Neuropeptide Y	NPY	Arcuate nuclei	Regulation of energy balance
Neurotensin		Hypothalamus; intestinal mucosa	May act as a neurohormone
Orexin A and B		Lateral hypothalamic area	Regulation of energy balance/food intake
Prolactin-inhibitory factor (Dopamine)	PIF (DA)	Arcuate nuclei	Inhibits PRL secretion
Prolactin-releasing hormone		Paraventricular nuclei	Stimulates release of PRL from anterior pituitary
Substance P	SP	Hypothalamus, CNS, intestine	Transmits pain; increases smooth muscle contractions of GI tract
Thyrotropin-releasing hormone	TRH	Paraventricular nuclei	Stimulates release of TSH and PRL from anterior pituitary
Urocortin		Lateral hypothalamus	CRH-related peptide
Cocaine and amphetamine-related transcript	CART	Hypothalamus; other brain regions	Involved in reward, food intake

(continued on inside back cover)

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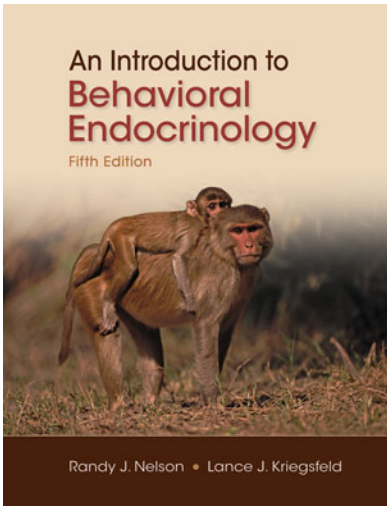

The Cover

Rhesus macaque, *Macaca mulatta*, female carrying young, Keoladeo Ghana National Park, India. © Bernard Castelein/ Nature Picture Library/Alamy Stock Photo.

An Introduction to Behavioral Endocrinology, Fifth Edition

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For our family and friends…

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Preface

It is July 2016 as we submit the final pieces and parts of this book manuscript. The First Edition of this book was published over 20 years ago, and there have been many changes in the field and in this textbook over the past several editions. A co-author, Lance Kriegsfeld, has been added to this Fifth Edition of the book. Dr. Kriegsfeld joined Dr. Nelson's lab shortly after the First Edition was published, and has been deeply involved with subsequent editions. He is now a professor at UC Berkeley, occupying a faculty position in the same department in which Frank Beach, the founder of this field, spent much of his career. Dr. Kriegsfeld teaches the descendent of Dr. Beach's *Hormones and Behavior* course at Berkeley that enrolls over 250 students annually.

Behavioral endocrinology is a truly interdisciplinary field. It involves the study of phenomena ranging from genetic, molecular, and cellular levels of analysis to the study of individual and social behaviors. We had several goals when we began writing the Fifth Edition of this textbook, one of which was to continue to present information about the interactions between hormones and behavior from an interdisciplinary perspective. In an effort to provide students with information about the scientists who laid the foundation for modern studies of behavioral endocrinology, we presented current hypotheses and theories in the context of their historical origins. Naturally, after more than six years since the publication of the Fourth Edition, every chapter needed general updating to reflect recent developments, research, and studies in the field. Some areas, such as body mass regulation and circadian rhythm research, are moving forward with rapid advances announced weekly.

One criticism of the book received in the past, especially from our colleagues teaching in Psychology departments, is that there is too much comparative work in the text. This is a criticism that we continue to happily ignore. The comparative perspective is what gives behavioral endocrinology great strength, and has revealed some of the most fascinating discoveries in our field using nontraditional animal models. We present this broad comparative approach in this edition. It is our hope that presenting adaptive function along with molecular and physiological mechanisms will yield greater understanding than presenting either approach alone.

We both have taught this course out of Psychology departments and thus appreciate that many behavioral endocrinology students will be psychology majors. Thus, we have tried to keep the conceptual issues clear, and provide only sufficient details and examples that support the concepts. New to this edition are learning objectives and highlights of the main points for each chapter to help guide students through the text. We also added a marginal glossary so students can easily find definitions for key terms as they read. Based on our teaching experience with this

course, we assume that psychology students will have taken a course in biopsychology or behavioral neuroscience by the time they encounter this textbook, but again, we have tried to keep discussions of endocrine physiology and biochemistry to a minimum level necessary to understand the hormone–behavior interactions being discussed. Because students are likely to be familiar with the behavior of common animals such as dogs and rabbits, we have continued to use them as examples to help explain many concepts in this text. This edition is supported by a student website that contains some wonderful videos and animations, which we hope help illustrate some of the behavioral and physiological concepts discussed in the text. We have continued to use and enhance color graphics that we hope will help clarify principles discussed.

Several topics had to be omitted or curtailed in the text. We assume that professors will use additional readings to make up for any deficiencies. Some topics covered in the text are controversial and will likely stimulate class discussions. At the end of each chapter are some questions for discussion that we hope will be potential starting points for such exchanges. An updated list of suggested readings is also provided at the end of each chapter where students can find reasonably current and more detailed information on the material in each chapter.

This is a very exciting time to be studying this field, either as a student or as a researcher in behavioral endocrinology. We hope that we have captured for the reader at least some fraction of the excitement of this field that we both have enjoyed.

Randy J. Nelson
Lance J. Kriegsfeld
July 2016

Acknowledgments

Completion of a textbook requires input from students, colleagues, editors, artists, production editors, photo editors, composers, and friends. There are so many people to thank who provided remarkable assistance to us as we worked on this edition. We remain profoundly grateful to the reviewers and colleagues who provided feedback and assistance that shaped all of the textbook editions. These individuals include: Elizabeth Adkins-Regan, Noah Ashley, Gregory Ball, Cydni Baker, Jacques Balthazart, Tim Bartness, Andy Bass, Tracy Bedosian, George Bentley, Dan Bernard, Staci Bilbo, Eric Bittman, Elliott Blass, Jeff Blaustein, Joan Blom, Jeremy Borniger, Robert Bridges, Sue Carter, Joe Casto, Frances Champagne, Silvana Chiavegatto, Yasmine Cisse, Nicky Clayton, Lique Coolen, Tara Craft, David Crews, James Dabbs, Greg Demas, Courtney DeVries, Don Dewsbury, Gary Dohanich, Debbie Drazen, Lori Flanagan-Cato, Alison Fleming, Laura Fonken, Nancy Forger, Karyn Frick, Stephen Gammie, Monica Gaudier-Diaz, Erica Glasper, Paul Gold, Bruce Goldman, Jim Goodman, Neta Gotlieb, Elizabeth Gould, David Gubernick, Achikam Haim, Tom Hahn, Joyce Hairston, Eric Herzog, Andrew Hotchkiss, Elaine Hull, Kim Huhman, Kim Jennings, Ellen Ketterson, Veronica Kim, Sabra Klein, Kelly Klump, Rosemary Knapp, Michael Leon, Al Lewy, Joe Lonstein, Vicky Luine, Robert Mason, Margaret McCarthy, Martha McClintock, Jim McGaugh, Lynn Martin, Chris Moffatt, Celia Moore, Ignacio Moore, Michael Moore, John Morris, Gretchen Neigh, Mai Nguyen, Karl Obrietan, Kathie Olsen, David Olton, Deb Olster, Vladimir Pravosudov, Brian Prendergast, Leah Pyter, Emilie Rissman, Mike Romero, Jay Rosenblatt, Ed Roy, Heather Rupp, Ben Sachs, Randall Sakai, Jen Sartor, Jill Schneider, Barbara Sherwin, David Shide, Rae Silver, Cheryl Sisk, Benjamin Smarr, Chuck Snowdon, Emilio Soto-Soto, Judith Stern, Brian Trainor, Anjali Trasy, Sari van Anders, George Wade, William Walker, James Walton, Gary Wenk, John Wingfield, Amy Wisniewski, Ruth Wood, Pauline Yahr, Kelly Young, Zachary Weil, and Irving Zucker.

We are especially grateful for assistance during the preparation of this Fifth Edition by many colleagues, who provided helpful, insightful, direct, critical, and immensely kind comments, including Elizabeth Adkins-Regan, Jill Becker, Laura Carruth, Ann Clark, Yvon Delville, Bryan Jones, Kimberly Kinzig, Benedetta Leuner, Farrah Madison, Luke Remage-Healey, Wendy Salzman, Beth Wee, and Susan Zup.

We attempted to incorporate virtually all of these reviewers' suggestions for changes into the various editions. Occasionally, because of stubbornness, laziness, or other negative traits on our part, we failed to address our friends' and colleagues' suggestions. Any and all remaining errors, sources of confusion, or other shortcomings in this new edition remain our responsibility.

We are especially grateful to our many colleagues who kindly provided reprint or preprint copies of their papers, as well as our colleagues and friends who generously provided permission to use their graphic or photographic material in the book or website.

We also thank the very hard-working folks at Sinauer Associates. Although only our names appear on the cover, this book is the result of enormously helpful and talented people. Dr. Nelson remains grateful for the friendship and guidance provided to him during the first two editions by Pete Farley, and during production of the Third Edition by Graig Donini. Graig started the Fourth Edition of this book, but it was completed by the remarkably kind and talented book editor, Sydney Carroll, who has gently nudged this Fifth Edition into existence.

We are grateful to Kathaleen Emerson and Alison Hornbeck, the production editors, whose attention for detail helped improve the book. Others who deserved special thanks at Sinauer include Chris Small, production manager; Janice Holabird, book designer and compositor; Elizabeth Morales, artist; David McIntyre, photo editor. We are grateful to Lou Doucette, our copy editor, who gently repaired our text. We also thank Jason Dirks, the media and supplements editor, for his help in designing, creating, and maintaining the website. This Fifth Edition of the textbook is much improved because of their unrelenting hard work and uncompromising standards.

Finally, we thank the hundreds of undergraduate students who have taken our courses in Behavioral Endocrinology over the past several decades. They have provided many helpful suggestions on improving the textbook. The study of the interactions among hormones, brain, and behavior is a fascinating field. If we were able to convey just a small part of the excitement in this discipline to students, then we'll both consider this book a success.

Media and Supplements

to accompany *An Introduction to Behavioral Endocrinology*, Fifth Edition

For the Student

Companion Website

sites.sinauer.com/be5e

The Companion Website provides a variety of resources to help students learn the material and to illustrate some of the behaviors and concepts discussed in the text. The site includes:

- **Animations**: Detailed animations explain selected complex concepts and processes
- **Videos**: Segments that illustrate interesting behaviors in a variety of organisms
- **Web Links**: Chapter-specific online resources, including articles, photographs, activities, and audio clips
- **Links** to journals, societies, and associations in the field of endocrinology
- A complete **Glossary**

For the Instructor

(Available to qualified adopters)

Instructor's Resource Library

The Instructor's Resource Library includes the following resources:

- **Textbook Figures & Tables**: Electronic versions of all the textbook's figures and tables (formatted and optimized for excellent legibility when projected) are provided in two formats: JPEGs and PowerPoint slides.
- **Test Bank**: Revised and expanded for the Fifth Edition, the Test Bank includes multiple-choice, short-answer, and essay questions for each chapter of the textbook. Prepared by the author, these questions are a helpful resource that can greatly speed the process of preparing exams and quizzes for the course.

Value Options

eBook

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The Study of Behavioral Endocrinology

1

Learning Objectives

The goal of this chapter is to introduce you to the rapidly growing field of behavioral endocrinology. By the end of this chapter you should be able to:

- define *behavioral endocrinology* and understand the historical roots of the field.
- define *hormones* and *behavior* and describe the general ways by which hormones and behavior interact.
- explain the various scientific techniques used to establish relationships among hormones, brain, and behavior.

Behavioral endocrinology is the scientific study of the interaction between hormones and behavior. This interaction is bidirectional: hormones can affect behavior, and behavior can influence hormones. **Hormones**, chemical messengers released from **endocrine glands**, travel through the blood system to influence the nervous system to regulate the physiology and behavior of an individual. Hormones change gene expression or the rate of cellular function, and they affect behavior generally by increasing the probability that a given behavior will occur in the presence of a specific stimulus. Hormones achieve this by affecting individuals' sensory systems, integrators, and/or effectors (output systems). Because certain chemicals in the environment can mimic natural hormones, these chemicals can profoundly affect the behavior of humans and other animals. Behavior is generally thought of as involving movement, but nearly any type of output, such as color change, can be considered behavior. A complete description of behavior is required before researchers can address questions of its causation. All behavioral biologists study a specific version of the general question "What causes individual A to emit behavior X?" Behavioral endocrinologists are interested

FIGURE 1.1 Lance Armstrong, seven-time Tour de France winner, was stripped of his titles and banned from cycling for life after not contesting charges leveled by the U.S. Anti-Doping Agency (USADA) that he used hormones, including anabolic steroids, to improve his performance.

in the interactions between hormones and behaviors. Usually these hormones are internal, but sometimes, the effects of hormone treatments or environmental contamination by hormones can significantly affect behavior.

Lance Armstrong won the grueling Tour de France bicycle race a record seven times between 1999 and 2005. No other bicyclist had come close to this achievement during the long history of this race. In 2012, however, the International Cycling Union president, Pat McQuaid, announced the decision to strip Armstrong of his seven Tour de France wins and banned him from the tournament for life, based on a report by the U.S. Anti-Doping Agency (USADA 2012a,b). This USADA report documented the use of performance-enhancing drugs during Armstrong's remarkable record-setting years. The use of anabolic steroids (testosterone) and other performance-enhancing hormones such as erythropoieten (EPO), as well as corticosteroids, was widely documented. Armstrong denied the allegations many times over the years but finally admitted that he used performance-enhancing drugs. Purists of the sport were offended by this hormonal "cheating" (**FIGURE 1.1**).

Questions arise from Armstrong's bicycling: Is there a connection between anabolic steroids and athletic performance? If taking hormones increases athletic performance, then why don't all athletes simply inject themselves with anabolic steroids to "level the playing field"? In other words, what are the costs, if any, of anabolic steroids? Most athletes do not want to take anabolic steroids such as EPO or testosterone. EPO is used in so-called doping of athletes; typically, EPO is released from the kidneys and stimulates red blood cell production in the bone marrow. Injecting EPO increases circulating red blood cells that provide additional oxygen to muscles and other tissues, which obviously provides an unfair advantage at high elevations (World Anti-Doping Agency, 2012). Testosterone is a steroid hormone that builds muscle mass. However, it is a controlled substance, and obtaining testosterone without a medical prescription is illegal. In addition to illegality, a number of undesirable side effects, including increased heart size (the heart is also a muscle) that decreases pumping efficiency, damage to the kidneys and liver, and compromised immune function, are important costs of taking these hormones. Several psychological problems have also been associated with anabolic steroid abuse, including feelings of paranoia, aggressive ideation, depression, and violent rage.

Armstrong's reported orchestration of the drug use by his U.S. Postal Service team and his threats of retaliation against several individuals are consistent with anabolic steroid abuse. We will explore the nature of the association between anabolic steroids and violent behavior more fully in Chapter 8. Can hormones really "hijack" the nervous system to influence behavior? Many people informally know that hormones differ between males and females and that hormones change rapidly during puberty, while many hormone concentrations decrease slowly as folks age. Questions about the relationship between hormones and behavior arise in many circumstances. For example, is the sex drive of adolescents higher than the sex drive of adults? Is the sex drive of women higher or lower than the sex drive of men? Is sexual behavior of women influenced by menopause? Is homosexuality caused by hormone concentrations that are too low or too high? Why are men much more likely than women to commit violent crimes? How does exposure to acute or chronic stressors affect learning and memory? Can melatonin cure jet lag? Do seasonal cycles of depression occur in people? Does postpartum depression really exist? Can leptin or other hormones curb our food intake? You may have discussed these and other questions about hormones and behavior casually with your friends and family members. Researchers in the field of behavioral endocrinology attempt to address these kinds of questions in a formal, scientific manner. In contrast to popular beliefs, hormones do not cause behavioral changes per se; that is, hormones

behavioral endocrinology The study of the interactions among hormones, brain, and behavior.

hormone An organic chemical messenger released from endocrine cells that travels through the blood system to interact with cells at some distance away and causes a biological response.

endocrine glands A ductless gland from which hormones are released into the blood system in response to specific physiological signals.

do not hijack the nervous system to influence behavior. Rather, hormones change the probability that a specific behavior will occur within the appropriate behavioral or social context. What constitutes an appropriate context is typically subject to social and cultural learning.

Historical Roots of Behavioral Endocrinology

The study of the interaction between hormones and behavior has been remarkably interdisciplinary since its inception; methods and techniques from one scientific discipline have been borrowed and refined by researchers in other fields. Psychologists, endocrinologists, neuroscientists, entomologists, zoologists, geneticists, molecular and cellular biologists, anatomists, physiologists, behavioral ecologists, psychiatrists, and other behavioral biologists have all made contributions to the understanding of hormone-behavior interactions. This exciting commingling of scientific interests and approaches, with its ongoing synthesis of knowledge, has led to the emergence of behavioral endocrinology as a distinct and important field of study (Beach, 1975b). The scientific journal *Hormones and Behavior* began publication in April 1967, and a scientific organization devoted to the study of hormones and behavior, the Society for Behavioral Neuroendocrinology, was founded in 1996. Both the journal and scientific society are growing.

Ebbinghaus (1908) stated that **psychology** has a short history but a long past, and the same can be said of behavioral endocrinology (Beach, 1974a). Although the modern era of the discipline is generally recognized to have emerged during the middle of the twentieth century with the publication of the classic book *Hormones and Behavior* (Beach, 1948), some of the relationships among the endocrine glands, their hormone products, and behavior have been implicitly recognized for centuries.

psychology The scientific study of emotion, cognition, and behavior.

testes The male gonads, which produce steroid hormones and sperm.

castration The surgical removal of the gonads.

eunuch A man who has been castrated (testes removed).

The male sex organs, or **testes**, produce and secrete a hormone called testosterone that influences sexual behavior, aggression, territoriality, hibernation, and migration, as well as many other behaviors that differentiate males from females. The testes of mammals are usually located outside the body cavity and can easily be damaged or removed. Thus, **castration**, the surgical removal of the testes, has historically been the most common manipulation of the endocrine system. For millennia, individuals of many species of domestic animals have been castrated to make them better to eat or easier to control, and the behavioral and physical effects of castration have been known since antiquity (**FIGURE 1.2**). Indeed, these effects were known to Aristotle, who described the effects of castration in roosters (and humans) with great detail and accuracy. For example, in *Historia Animalium*, written about 350 BCE, Aristotle reported:

> *Birds have their testicles inside.… Birds are castrated at the rump at the part where the two sexes unite in copulation. If you burn this area twice or thrice with hot irons, then, if the bird be full-grown, his crest grows sallow, he ceases to crow, and foregoes sexual passion; but if you cauterize the bird when young, none of these male attributes or propensities will come to him as he grows up. The case is the same for men: if you mutilate them in boyhood, the later-growing hair never comes, and the voice never changes but remains high-pitched; if they be mutilated in early manhood, the late-growths of hair quit them except the growth on the groin, and that diminishes but does not entirely depart.*

FIGURE 1.2 St. Philip the Evangelist baptizing a eunuch This biblical painting by Rembrandt (1606–1669) indicates that the relationship between the missing testes and behavior was understood for centuries.

For centuries, royalty employed men castrated before puberty, called **eunuchs**, to guard women from other men. For example, the Old Testament reports that these emasculated males were used to guard the wom-

FIGURE 1.3 Eunuch of the last imperial court of China, photographed by Henri Cartier-Bresson in 1949. Note the lack of facial hair and unusually long arms.

en's quarters of Hebrew kings and princes (Esther 1:10). Castration in humans often has little or no effect on physical appearance or future sexual behavior when performed after the unfortunate individual attains sexual maturation; however, if human males are castrated before puberty, they will develop a characteristic physical appearance marked by short stature and long arms (**FIGURE 1.3**), and sexual behaviors are unlikely to develop. The typical secondary male sex characteristics are also affected by prepubertal removal of the testes. For example, as noted by Aristotle, eunuchs never develop beards, and the pubertal change in voice does not occur. Normally during puberty, the vocal cords of males thicken in response to testosterone secreted by the testes. It is the thickened vocal cords that produce the deeper-pitched voice characteristic of males, just as the thick strings of a guitar produce deeper-pitched notes than the thin strings.

Castration was once a common practice in Europe and Asia. Young boys with exceptional singing voices were castrated to prevent the pubertal changes in pitch. These singers became known as castrati. Although castrati were prized by church choirs for centuries, their popularity reached a peak in Europe during the seventeenth and eighteenth centuries with the development of opera, which made castrati the first superstars of the entertainment world (Heriot, 1974). The first castrato opera star, Baldassare Ferri, died in 1680 at the age of 70 with a fortune that was worth the equivalent of $3 million today. In hopes of attaining this level of wealth and fame, young boys with musical aptitude were identified early, and poor families offered their sons outright to church leaders, singing teachers, and music academies. Thousands of boys lost their testes but never gained the celebrity or riches of the star castrati.

What did a castrato sound like? Essentially, castrati had the range of a soprano, but the greater development of the male lungs gave their singing remarkable power. An early critic remarked, "Their timbre is as clear and piercing as that of choirboys and much more powerful; they appear to sing an octave above the natural voice of women. Their voices…are brilliant, light, full of sparkle, very loud, and astound with a very wide range" (Heriot, 1974).

After 200 years, the tastes of the opera-loving public changed. The rise in popularity of the female soprano voice reduced the demand for castrati, and they soon became an oddity. In 1849, the last great castrato, Giovanni Velluti, retired from opera to his villa in Venice. The last known castrato, Alessandro Moreschi, who served as the Sistine Chapel Choir's director, as well as one of its soloists, died in 1922. Before his death, he made 17 recordings that, although of poor quality by today's standards, still provide a remarkable example of this art form. Samples of these recordings can be found on this book's Companion Website (sites.sinauer.com/nelson5E).

FIGURE 1.4 Arnold Adolph Berthold of the University of Göttingen, who in 1849 published what is now recognized as the first formal experiment in endocrinology.

Berthold's Experiment

A useful starting point for understanding research in hormones and behavior is a classic nineteenth-century experiment that is now considered to be the first formal study of endocrinology. This remarkable experiment conclusively demonstrated that a substance produced by the testes could travel through the bloodstream and eventually affect behavior. Professor Arnold Adolph Berthold, a Swiss-German physician and professor of physiology at the University of Göttingen (**FIGURE 1.4**), demonstrated experimentally that a product of the testes was necessary for a cockerel (an immature male chicken) to develop into a normal adult rooster.

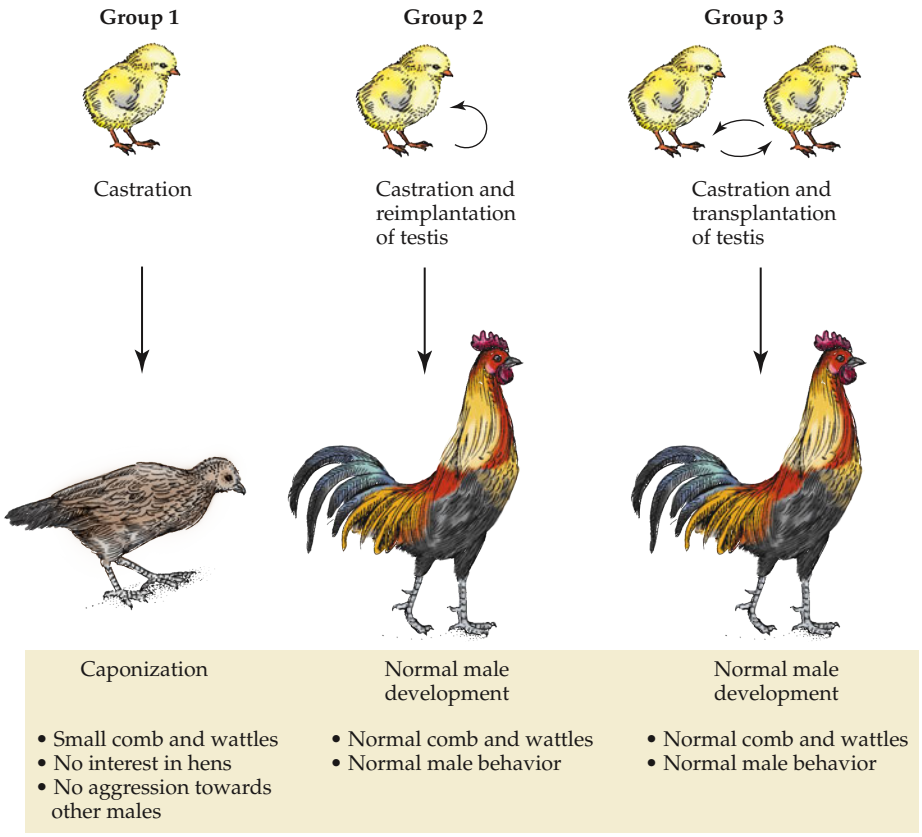


FIGURE 1.5 Berthold's experiment
The birds in Group 1 were castrated, and when observed several months later, they were smaller than normal roosters and failed to engage in rooster-typical behaviors. The birds in Group 2 were also castrated, but one of each bird's own testes was reimplanted in its abdominal cavity. These birds looked and behaved like normal roosters when adults. The two birds in Group 3 were castrated, and one testis from each bird was transplanted into the abdomen of the other. Several months later, these birds also looked and behaved like normal roosters. Berthold found that the reimplanted and transplanted testes in Groups 2 and 3 developed vascular connections and generated sperm.

As you know, roosters display several characteristic behaviors that are not typically seen among hens or immature chicks of either sex. Roosters mate with hens, they fight with other roosters, and of course, roosters crow. Moreover, roosters are larger than hens and immature birds and have distinctive plumage. On the other hand, capons, male chickens that have been castrated prior to adulthood in order to make their meat more tender, do not show many of the behavioral and physical characteristics of roosters. They do not attempt to mate with hens and are not very aggressive toward other males. Indeed, they avoid aggressive encounters, and if conditions force them to fight, they do so in a halfhearted manner. Finally, capons do not crow like roosters.

The behavioral and physical differences among roosters, hens, capons, and immature chickens were undoubtedly familiar to Berthold (Berthold, 1849a,b) (**FIGURE 1.5**). He placed six cockerels in three experimental groups, each consisting of two birds. He removed both testes from each of the two cockerels in the first group, and as expected, these birds eventually developed as capons. They never fought with other males after castration, and they failed to crow; instead, Professor Berthold reported, they developed the "monotone voice of the capon." They avoided females and never exhibited mating behavior. Finally, these birds looked different from intact (noncastrated) adult males; their bodies and heads were small, and their combs and wattles were atrophied and pale in color.

The second pair of cockerels was also castrated, but Berthold reimplanted one testis from each bird in its abdominal cavity after ensuring that all of the original vascular and neural connections had been cut. Interestingly, both birds in this group developed normal rooster behavior. According to Berthold, they "crowed lustily, often engaged in battle with each other and with other cockerels, and showed the usual reactions to hens." Their physical appearance was indistinguishable from

that of other young roosters; they grew normally and possessed highly developed combs and wattles that were bright red in color.

The remaining two birds were also castrated, but after the testes were removed, Berthold placed a single testis from each bird in the other's abdominal cavity. Like the cockerels in the second experimental group, these birds also developed the "voice, sexual urge, belligerence, and growth of combs and wattles" characteristic of intact males.

After observing all six birds for several months, Berthold dissected one of the cockerels from the second group and found that the implanted testis had attached itself to the intestines, developed a vascular supply, and nearly doubled in size. Eventually, he examined all the implanted testes under a microscope and noted the presence of sperm.

Based on the results of this experiment, Berthold drew three major conclusions: (1) the testes are transplantable organs; (2) transplanted testes can function and produce sperm (Berthold drew the analogy to a tree branch that produces its own fruit after having been grafted to another tree); and (3) because the testes functioned normally after all nerves were severed, there are no specific nerves directing testicular function. To account for these findings, Berthold proposed that a "secretory blood-borne product" of the transplanted testes (*productive Verhältniss der Hoden*) was responsible for the normal development of the birds in the second and third groups. It is worth noting that three of the four parameters Berthold used to formulate this hormonal hypothesis—mating, vocalization, aggression, and distinctive appearance—were behavioral.

In recent years, Berthold's experiment has been credited as the genesis of the field of endocrinology (and of behavioral endocrinology: **BOX 1.1**), but Berthold's intriguing demonstration of nonneural control of behavior was apparently not embraced with any enthusiasm by his scientific contemporaries; we find no citations to his paper for nearly 60 years after its publication. Berthold previously authored a well-known physiology textbook and had actively conducted research. His textbook makes it apparent that Berthold was a proponent of the pangenesis theory of inheritance. This theory, endorsed by many biologists prior to the discovery of how chromosomes and genes function, held that all body parts actively discharge bits and pieces of themselves into the blood system, where they are transported to the ovaries or testes and assembled into miniature offspring resembling the parents. Because of this theoretical stance, Berthold had two concepts at hand when evaluating the results of his testicular transplantation study: (1) various parts of the body release specific agents into the blood, and (2) these agents travel through the bloodstream to particular target organs. Why Berthold did not go any further with his interesting finding is not known; he died 12 years later in 1861 without following up on his now-famous study.

What Are Hormones?

Berthold took the first step in the study of behavioral endocrinology by demonstrating that the well-known effects of the testes were due to their production of a substance that circulated in the blood. Modern studies in behavioral endocrinology have documented the effects of substances from many different glands affecting an increasing number and range of behaviors.

We now know Berthold's "secretory blood-borne product" as a hormone, a term coined by Ernest Starling during a lecture in 1905. Previously, in 1902, Starling and fellow British physiologist William Bayliss identified a chemical messenger secreted by the duodenum that stimulated pancreatic secretions in dogs, a process previously considered to be regulated by the nervous system by Ivan Pavlov, a physiologist best known for his discovery of classical conditioning.

Hormones are released from these glands into the bloodstream (or the tissue fluid system in invertebrates), where they may then act on target organs (or tissues) at some distance from their origin. Hormones coordinate the physiology and

BOX 1.1 *Frank A. Beach and the Origins of the Modern Era of Behavioral Endocrinology*

For some time before behavioral endocrinology emerged as a recognized field, its foundations were being laid by researchers in other fields. The anatomists, physiologists, and zoologists who were doing the majority of the work on "internal secretions" prior to 1930 often used behavioral end points in their studies. Soon thereafter, psychologists began making important contributions in the study of hormones and behavior. In the early decades of the twentieth century, American psychology was undergoing a major change, both in ideology and methodology. Led by John B. Watson, students of the "science of the mind" were casting aside introspection as a method in favor of observation and experimentation. Watson argued that only overt behavior was observable, and psychologists began describing and quantifying all types of overt behavior.

Karl S. Lashley did his graduate work under Watson at the Johns Hopkins University and eventually joined the faculty at the University of Chicago. Lashley investigated the effects of removing parts of rats' brains to discover where in the brain various psychological processes were carried out; he was particularly interested in finding where memories were stored. Although he never published any reports on the interaction between hormones and behavior, Lashley was clearly interested in the subject (e.g., Lashley, 1938), and several of Lashley's students became important contributors to behavioral endocrinology, including Calvin P. Stone, Josephine Ball, and Frank A. Beach.

Beach, William C. Young (see Box 3.2), and Daniel Lehrman (see Box 7.1) were especially influential during the early studies of behavioral endocrinology. Beach's dissertation at Chicago, "The Neural Basis for Innate Behavior," examined the effects of cortical tissue destruction on the maternal behavior of first-time mother rats. In 1937, Beach began working as a curator in the Department of Experimental Biology at the American Museum of Natural History in New York and began contributing to the museum's tradition of comparative behavioral experimentation. One study completed at the museum, which was a logical extension of Beach's dissertation work, is of special note: he began investigating the effects of cortical lesions on the mating behavior of male rats. Some brain-damaged rats continued to mate, whereas others failed to do so. Beach was concerned that his lesions were interfering indirectly with the endocrine system, so he injected the nonmating brain-injured rats with testosterone, the primary hormone secreted from the testes. The treatment evoked mating behavior in some of the lesioned rats, and this modification of behavior by hormones prompted Beach to learn more about endocrinology.

Frank A. Beach (1911–1988)

Beach audited a course in endocrinology at New York University but was distressed by the lack of information about the behavioral effects of hormones; the professor responded to Beach's complaint by allowing him to teach one session. While preparing for the lecture, Beach discovered that no comprehensive summary of hormone-behavior interactions existed, and he prepared such a review as a term paper for the endocrinology course. Several years later, Beach expanded his paper into an influential book, *Hormones and Behavior* (Beach, 1948). The publication of this book marked the beginning of the formal study of behavioral endocrinology. Beach is credited with the genesis of this scientific discipline, and he continued to provide intellectual leadership in shaping the field for the next 40 years.

behavior of an animal by regulating, integrating, and controlling its bodily function. For example, the same hormones that cause gametic (egg or sperm) maturation also promote mating behavior in many species. This dual hormonal function ensures that mating behavior occurs when animals have mature gametes available for fertilization. Another example of endocrine regulation of physiological and behavioral function is provided by the metabolic system. Several metabolic hormones work together to elevate blood glucose levels prior to awakening, in anticipation of

BOX 1.2 *Neural Transmission versus Hormonal Communication*

Although neural and hormonal communication both rely upon chemical signals, several prominent differences exist. Communication in the nervous system is analogous to traveling on a train. You can use the train in your travel plans as long as tracks exist between your proposed origin and destination. Likewise, neural messages can travel only to destinations along existing nerve tracts. Hormonal communication, on the other hand, is like traveling in a car. You can drive to many more destinations than train travel allows, because there are many more roads than railroad tracks. Likewise, hormonal messages can travel anywhere in the body via the circulatory system; any cell receiving blood is potentially able to receive a hormonal message.

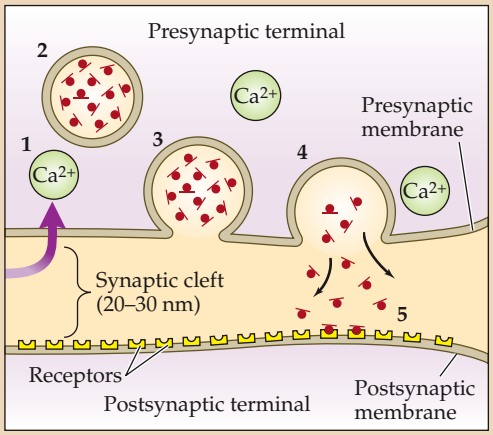
Neural and hormonal communication differ in other ways as well. To envision them, consider the differences between digital and analog technologies. Neural messages are digital, all-or-none events that have rapid onset and offset: neural signals can take place in milliseconds. Accordingly, the nervous system mediates changes in the body that are relatively rapid. For example, the nervous system regulates immediate food intake and directs body movement. In contrast, hormonal messages are analog, graded events that may take seconds, minutes, or even hours to occur. Hormones can mediate long-term processes, such as growth, development, reproduction, and metabolism.

Hormonal and neural messages are both chemical in nature, and they are released and received by cells in a similar manner; however, there are important differences as well. As shown in the figure in (A), in response to the arrival of a neural impulse at a presynaptic terminal, there is an influx of calcium ions (Ca^{2+}) (1) that causes vesicles (2) containing neural chemical messages called neurotransmitters to move toward the presynaptic membrane. The vesicles fuse with the membrane (3) and release the neurotransmitter into the synaptic cleft (4). The neurotransmitters travel a distance of only 20–30 nanometers (30×10^{-9} m) to the membrane of the postsynaptic neuron, where they bind with receptors (5). As shown in the figure in (B), hormones manufactured in the Golgi apparatus of an endocrine cell (1) also move toward the cell membrane in vesicles (2) that fuse with the membrane, releasing the hormone (3). However, hormones then enter the circulatory system and may travel from 1 mm to 2 m (4) before arriving at a cell of a target tissue, where they bind with specific receptors (5).

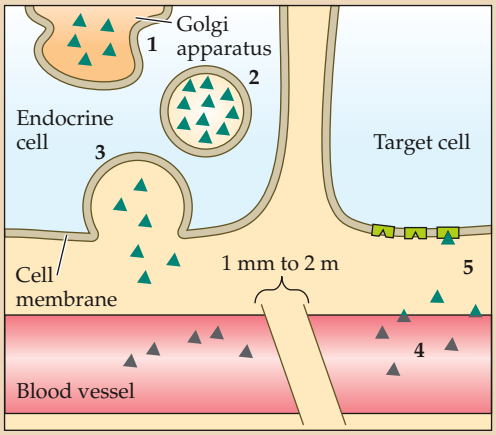
Another distinction between neural and hormonal communication is the degree of voluntary control that can be exerted over their functioning. In general, there is more voluntary control of neural than of hormonal signals. It is virtually impossible to will a change in your thyroid hormone levels, for example, whereas moving your limbs on command is easy.

Although these are significant differences, the division between the nervous system and the endocrine system is becoming more blurred as we learn more about how the nervous system regulates hormonal communication. A better understanding of the interface between the endocrine system and the nervous system is likely to yield important advances in the future study of the interaction between hormones and behavior.

(A) Neural transmission



(B) Hormonal communication



increased activity and energy demand. This "programmed" elevation of fuel availability coordinates the animal's physiology with its behavior.

Hormones are similar in function to **neurotransmitters**, the chemicals used by the nervous system in coordinating animals' activities. However, hormones can operate over a greater distance and over a much greater temporal range than neu-

neurotransmitters Chemical messengers that communicate between nerve cells (neurons).

rotransmitters (**BOX 1.2**). Hormones are also similar to **cytokines**, chemical signals produced by cells of the immune system, and may interact with cytokines to affect behavior, especially when individuals are ill or unduly stressed. Because of their structure, certain chemicals in the environment can mimic natural hormones and are generally referred to as endocrine disruptors. When such chemicals enter the food chain or water supply, they can affect the same hormone-behavior pathways as natural hormones. For example, about 16 million women in the United States use birth control pills. Much of the estrogen is secreted in their urine. According to the Freshwater Institute, part of Canada's Department of Fisheries and Oceans, the potent synthetic estrogens excreted by women taking hormone replacement therapy or birth control pills are not completely broken down during sewage treatment and are released into waterways (Kidd et al., 2007). Interestingly, the effects of these steroid hormones on reproductive development of wildlife and humans ingesting the water remain largely unspecified (Kidd et al., 2007). We will revisit the topic of endocrine disruptors' effects on behavior in subsequent chapters.

Importantly, not all cells are influenced by each and every hormone. Rather, any given hormone can directly influence only cells that have specific **receptors** for that particular hormone. Cells that have these specific receptors are called **target cells** for the hormone. The interaction of a hormone with its receptor begins a series of cellular events that eventually leads either to activation of enzymatic pathways or to effects on gene expression and protein synthesis. In the latter case, the newly synthesized proteins may activate or deactivate other genes, causing yet another cascade of cellular events. Recently, an additional mechanism has been reported; behavioral effects of hormones that are not caused by activation of the genetic machinery are called nongenomic effects of hormones on behavior and will be reviewed in Chapter 6.

Notably, sufficient numbers of appropriate hormone receptors must be available for a specific hormone to produce any effects. For example, if a capon had no receptors for testosterone, then implanting another testis (or giving testosterone hormone therapy) would not cause it to display testosterone-dependent traits. A common bias in behavioral endocrinology is the assumption that individual differences in the expression of a behavior reflect differences in hormone concentrations in the blood. In other words, it is assumed that roosters that fight frequently have higher blood testosterone concentrations than roosters that rarely fight. To a certain extent this assumption is correct. A minimal amount of hormone is required to activate sufficient receptors in neural networks to affect behavior; however, above that threshold, individual differences in hormone concentrations generally do not affect behavior. Individual differences in hormone-behavior interactions usually reflect complex influences of hormone concentrations, patterns of hormone release, numbers and locations of hormone receptors, and the efficiency of those receptors in triggering signal transduction pathways that ultimately affect gene transcription.

Hormones commonly alter the rate of normal cellular function. Another way that hormones can affect cells is to change their morphology or size. As mentioned, some athletes abuse anabolic steroids, which are synthetic hormones, because muscle cells grow larger after exposure to these substances. Hormones also may affect neuronal growth and development, as well as programmed cell death throughout the nervous system. Whereas the examples we have discussed so far have all demonstrated how the presence or absence of a hormone may affect behavior, it is important to appreciate that the interactive relationship between hormones and behavior is bidirectional: hormones obviously affect behavior, but, as we will see in subsequent chapters, behavior can also influence hormone concentrations and effects.

cytokine A protein chemical messenger that evokes the proliferation of other cells, especially in the immune system.

receptor A chemical structure on the cell surface or inside the cell that has an affinity for a specific chemical configuration of a hormone, neurotransmitter, or other chemical compound.

target cells A cell that has specific receptors for, and is affected by, a particular chemical messenger.

The Study of Behavior

Behavioral endocrinologists are interested in how the general physiological effects of hormones alter the development and expression of behavior and how behavior