Neurobiology, Endocrinology and Behavior☆

Elizabeth Adkins-Regan, Cornell University, Ithaca, NY, United States
C Sue Carter, Indiana University, Bloomington, IN, United States

Abstract

The experimental study of the physiological mechanisms of animal behavior, which began in the 1800s, has dual origins. Research on neural mechanisms, now referred to as behavioral neurobiology, neuroethology, or behavioral neuroscience, has its roots in comparative neuroanatomy, comparative physiology, and physiological psychology. Research on hormonal mechanisms, now known as behavioral neuroendocrinology, arose from endocrinology in addition to many other fields. With the realization that the nervous and endocrine systems are functionally connected, there has been increased integration within the field. Connections with several newer branches of science, such as molecular biology, have been established as well.

Keywords

Behavioral neurobiology; Behavioral neuroendocrinology; Comparative approach; History; Hormone; Neuroethology; Sexual behavior; Sexual differentiation; Social behavior.

Introduction

Two types of mechanisms, neural and hormonal, have been prominent in the history of research directed at uncovering the proximate physiological causes of animal behavior. During the first part of this history, the nervous and endocrine systems were envisioned as separate systems and were studied by somewhat different research communities. As a result, research on physiological mechanisms of animal behavior has tended to develop along two somewhat separate and parallel tracks. These dual origins are reflected in the organization of this survey. Beginning in the 20th century, several discoveries led to the realization that the nervous and endocrine systems are physiologically integrated to a highly significant extent, which is of great importance for animal behavior. Nerve cells can synthesize and secrete hormones; the behavioral effects of hormones are mediated by their actions on neurons, and the brain regulates the endocrine axes so that hormone levels related to behavior are responsive to both social and physical environments.

Origins of Behavioral Neurobiology: Sensory, Motor, and Motivational Systems in Comparative Perspective

The history of the study of the neural mechanisms of animal behavior is largely the history of neuroscience in a more general sense. The overarching motivation of the pioneers was often a desire to understand human minds and brains. However, because of the impossibility of doing experimental work with humans, investigations of animals have long played a significant role. The oldest and deepest scientific roots of the field are comparative neuroanatomy and comparative physiology. Then in the 20th century, developments in ethology led to the rise of neuroethology (also called behavioral neurobiology), which emphasized naturally occurring behavior in nondomesticated animals, while developments in psychology produced the subfield of physiological psychology, with its emphasis on learning, memory, and motivation in domesticated laboratory animals.

Comparative Neuroanatomy

Writing in the 1600s, René Descartes emphasized that the brain and nervous system are responsible for behavior. In subsequent centuries, many scientists examined and described the structure of the brain and nervous system in an array of animal species. A common theme was to note what seemed to be marked differences in the organization of the brain, especially the forebrain, and in the relative sizes of structures and brain divisions, and to speculate about their relationship to behavior and intelligence.

With the publication of Charles Darwin's theory of evolution by natural selection, these species differences in brain structure and size began to be interpreted in an evolutionary framework. Until the middle of the 1900s, the dominant view had been that the brains (especially forebrains) of different vertebrate classes (as represented by a small number of species from each of the largest classes) were fundamentally different in organization, that they formed an evolutionary series progressing toward the human brain, and that this series paralleled an increase in intelligence and behavioral complexity culminating in apes and humans.

☆*Change History*: September 2015. Elizabeth Adkins-Regan updated author affiliation and "Biography" section.

 doi:10.1016/B978-0-12-809633-8.01176-6

A set of scientific developments beginning in the 1950s and 1960s then led to a substantial revision of these ideas: a veritable intellectual revolution in comparative neuroanatomy. New methods for tracing the neural connectivity between brain regions revealed that the structure of different vertebrate brains had in fact been highly conserved over evolutionary time, with the same basic ground plan from fish to mammals (Striedter, 2005). The consequences of this revolution are still being felt, for example, in recent efforts to rethink and rename the structures of the avian brain (Reiner, 2005). Another key development was the realization that phylogenetic relationships are tree-like, rather than ladder-like. As this more modern view of phylogeny was absorbed into comparative neuroanatomy and comparative animal behavior, efforts were made to expunge the remnants of teleological thinking (evolution as a guided progression toward human superiority) from the field as well (Hodos and Campbell, 1969). Tree thinking, along with improved methods for taking appropriate account of body size in the comparative study of brain size, led to the realization that large brains and large forebrains had evolved several times independently in vertebrates, and that mammals do not have larger brains than all other vertebrates when corrected for body size (Striedter, 2005). This repeated convergent evolution of large brains then allowed researchers to more rigorously test hypotheses about the ecological or behavioral characters that are associated with large brains (long-distance migration? predatory foraging? group living and social life?). Such characters provide clues to the selective pressures for increases in brain size: a line of research that continues to be active. New methods for determining phylogenetic trees from molecular information and for statistically analyzing comparative data in a phylogenetic framework have increased the power and objectivity of the comparative approach to such hypothesis testing.

The popular world, and the neuroscientific world as well, have been slow to absorb this revolution, however. One still sees the words "lower" and "higher" applied to animal species. The incorrect assumption that nonmammals lack the forebrain structures of intelligent learning and therefore are largely "instinctive" creatures is still widespread.

Comparative Physiology

Among his many other intellectual pursuits, Descartes was interested in whether and how (through what bodily processes) behaving animals were different from mechanical toys and automata. It was Descartes who developed the concept of the spinal reflex and proposed specific neural pathways for reflexive actions such as withdrawing a limb from fire. It was not until the late 1800s, however, that it was discovered (by Santiago Ramón y Cajal) that the nervous system consists of cells (neurons): an achievement for which he shared a Nobel Prize with Camillo Golgi in 1906. The studies of another Nobel Prize laureate, Charles Sherrington (**Fig. 1**) (who originated the term synapse and won the Nobel Prize in 1932), were the beginning of a long and productive line of research on the nature of reflexes and their underlying neuronal activity. Among other discoveries, it was found that a rich array of biologically significant reflexes and even more complex actions still occurred in spinal and decerebrate preparations. The reflex concept remained an essential part of the neurobiology of behavior for several decades. It is still the case that some behaviors important for survival (e.g., coughing or withdrawing a limb from a sharp object) are best thought of as reflexes, along with all the stretch reflexes that posture and locomotion require. Spinal reflexes of mammals were found to include sexual reflexes such as ejaculation or estrous postures, raising questions about whether hormones act at the level of the spinal cord and the brain: one of many signs of the bridge forming between research on neural and hormonal mechanisms.

Fig. 1 Sir Charles Sherrington. © The Nobel Foundation 2009.

In 1786, Luigi Galvani discovered that muscle twitches and nerve function have an electrical basis, and in 1870, Fritsch and Hitzig found that weak electrical stimulation of the dog cortex produced muscle movements on the opposite side of the body. In subsequent decades, the neurophysiological approach to behavioral mechanisms flourished as parallel advances occurred in the apparatus for recording from and stimulating single and multiple neurons (e.g., amplifiers and oscilloscopes) and in the animal preparations themselves (e.g., J.Z. Young's discovery of the giant motor axon of squid). Especially exciting for those with a keen interest in animal behavior was the development of methods for stimulating or recording from the brains of freely moving animals. The studies of Walter Hess (**Fig. 2**) (a 1949 Nobel Prize winner) in cats showed that a variety of normal appearing actions occurred following brain stimulation, including going to sleep, an early sign of the role of brain activity in this biologically important behavior. Recent years have seen the rapid development of new techniques for recording from multiple neurons and for manipulating neurons in order to establish their causal role in behavior (Jorgenson *et al.*, 2015).

Although not as technically sophisticated as neurophysiology, the use of ablations or lesions of specific brain regions has long been an important tool for testing hypotheses about the causal relation between the function of a region and the expression of a behavior. Marie Jean Pierre Flourens originated this experimental approach to the study of the brain in the 1820s, establishing through a systematic program of circumscribed ablations in rabbits and pigeons that damage to different brain divisions has different effects on behavior. For example, an ablation in a deep cerebellar layer produced locomotor deficits in pigeons, whereas an ablation of a part of the midbrain (in what then came to be called the optic lobe) caused blindness. Lesions are still a valuable stage of a brain and behavior research program, and technical improvements now permit lesions that are small, neurochemical (affecting only a subset of neurons such as dopaminergic neurons), or even reversible (e.g., temporary inactivation with lidocaine).

Neuroethology (Behavioral Neurobiology)

The work of ethologists on mechanisms of behavior tended to focus on nonphysiological mechanisms such as sensory cues, and much of what was referred to as behavioral physiology by this community did not actually go inside the animal, but instead used its responses to external cues to conceptualize internal processes. As recently as 1966, Peter Marler and William J. Hamilton's textbook *Mechanisms of Animal Behavior* contained rather little information about any neural mechanisms (Marler and Hamilton, 1966). Concepts such as releasing stimulus or hunger drive, and models such as Tinbergen's hierarchical model of instinct, were clearly meant to reflect some kind of neural processes, but explicit links to those were seldom proposed. A few researchers began to explore those links, however. For example, Erich von Holst and Ursula von St. Paul electrically stimulated the brains of freely moving chickens, producing behavior such as vocalization, grooming, feeding, and aggressive attack. These investigations were explicitly aimed at understanding the neural basis of drive. Jerram Brown and Robert Hunsperger used a similar method to study the neural basis of aggression in cats and applied the term neuroethology to such research.

Subsequent years saw the flowering of a very active research interest in the study of the neural mechanisms for the ecologically relevant adaptive behavior of nondomesticated animals such as insects (crickets, locusts, cockroaches), toads, and bats (Roeder, 1967; Ewert, 1980; Zupanc, 2004). This particular marriage of comparative physiology with animal behavior is what is sometimes

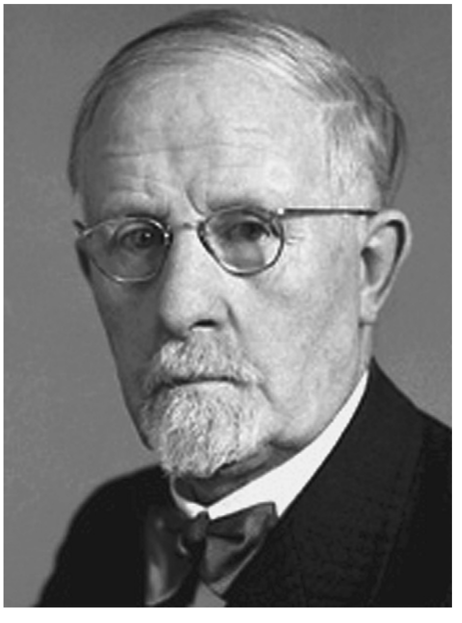

Fig. 2 Walter Hess. © The Nobel Foundation 2009.

meant today by the terms neuroethology or behavioral neurobiology. The emphasis has been on sensory processes and motor output, and a number of these lines of research have become classics of animal behavior.

The neurophysiological approach has been prominent, and Theodore Bullock (Fig. 3) in particular did much to ensure that neurophysiology would be comparative, directed at a diverse array of animals.

With respect to sensory processes, neuroethologists discovered and analyzed several previously unknown sensory systems, such as acoustic reception by moths and electroreception by weakly electric fish (the latter by Bullock, who also found the infrared receptors of pit vipers). They explored animals' abilities to detect stimuli out of the range of human detectability, for example, ultrasonic hearing by bats, ultraviolet wavelength vision by birds, and the exceptional binaural ability of owls when locating small prey by sound. These discoveries have reinforced the ethologists' insight that understanding an animal's umwelt is critical to an understanding of its behavior.

The classic neuroethological studies of motor processes produced several key concepts and discoveries about how the nervous system works. The importance of inhibition as well as excitation became apparent. Actions that have to occur very rapidly for the animal to survive (e.g., escape from a predator) could be triggered by the activity of a very small number of command neurons. Even in a vertebrate (a fish), the escape response was found to be triggered only by two very large cells, the Mauthner cells. Studies by Donald Wilson of locust flight revealed the existence of a central pattern generator (also called oscillator or pacemaker), the neural elements that produce rhythmic firing leading to rhythmic muscle movement even in the absence of stimulus inputs or any feedback from the periphery. It had been known since at least 1914 (through studies by T. Graham-Brown) that no proprioceptive input was needed for a dog's locomotor or scratch reflexes. Such central pattern generators might need an initial stimulus to get them going, and their exact frequency might be modulated by external stimuli, but the basic rhythmic pattern was clearly organized centrally, rather than resulting from a chain or sequence of stimulus–response reflexes. In a similar vein, the existence of endogenous circadian clocks became convincingly established, and so-called master clocks were then localized in the nervous system of an insect (in the subesophageal ganglion of a cockroach) in the late 1950s by Janet Harker and subsequently in the diencephalic suprachiasmatic nuclei of rats in the 1970s by Robert Moore and Victor Eichler and by Friedrich Stephan and Irving Zucker. Another set of key motor system concepts, developed by von Holst and Horst Mittelstaedt, were efference copy and reafference. Motor command signals are copied to another region of the nervous system where they can be compared to sensory feedback resulting from the motor performance. Processes of this kind allow the animal to tell the difference between active and passive movement (e.g., between moving vs. being windblown) and to avoid interference between sensory cues from the individual's own emissions versus echoes or emissions from other individuals (as in bats using ultrasound to catch insects). All these concepts have proven to be of enduring value in understanding how nervous systems produce adaptive behavior.

Physiological Psychology

The science of psychology has long sought to understand the behavior of all animals, not just humans. Early generations of comparative psychologists studied a highly diverse array of animals, including microbes, invertebrates, and vertebrates from all the larger classes (Washburn, 1936). Physiological psychologists took the understanding of the neural and other physiological bases of behavior as their mission. Early on, and continuing up to the present, there was great interest in using the lesion method to study learning and memory. An important article was the research of Lashley (1963) on cortical lesions and memory for learned tasks in

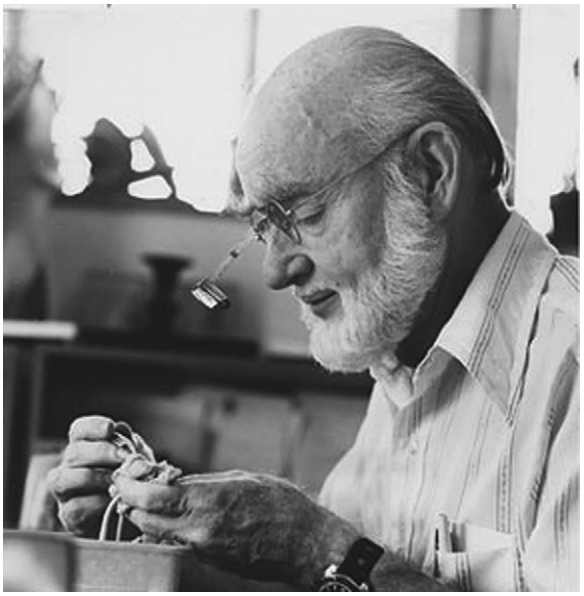

Fig. 3 Theodore Bullock. With permission from the Scripps Institution of Oceanography, University of California – San Diego.

rats – his search for the engram. He found that task memory did not seem to be located in any particular place in the cortex. Instead, how much cortex was damaged predicted whether and how much memory was lost. At the time this may have seemed like a failure to find the engram, but subsequent decades have revealed a great truth in his findings: the cortex works in a distributed manner. The secret of learning and memory is now thought to lie in part in the structural and functional plasticity of neurons and their connections: a concept originated by Donald Hebb in the 1940s (Hebb, 1949).

The 1950s and 1960s were a time of great interest in the hypothalamus and its role in motivated behavior of basic survival significance such as hunger, drinking, and regulation of temperature (Stellar, 1954). Pictures of obese rats with lesions of the ventromedial hypothalamus are still compelling textbook images. Such research has taken on new significance recently with the occurrence of a pandemic of obesity in humans.

In recent decades, brain-oriented physiological psychology has become known as behavioral neuroscience. Additional brain regions such as the amygdala and prefrontal cortex have been thoroughly explored in relation to behavior. Their roles have been established in emotional responses such as fear (amygdala) and in cognitive functions such as switching problem solving strategies (prefrontal cortex). One of the most notable developments in the science of animal behavior has been a convergence of interest between behavioral neuroscientists and neurobiologists in neural mechanisms for use of space and memory for spatial locations. This line of research has produced insights into the role of hippocampal neurons in performance of rats in mazes, in memory for locations of stored food items in scatter hoarding birds, and in homing by pigeons (Bingman, 1992; Sherry, 1997; Eichenbaum, 2017).

Origins of Behavioral Neuroendocrinology: Social and Reproductive Behaviors

In the last quarter of the 20th century, the biologist Wilson (1998) argued for a "new synthesis" or "consilience" ("jumping together of knowledge by the linking of facts and fact-based theory across disciplines"). The wisdom of this approach is especially relevant to the behavioral neuroendocrinology of social and reproductive behaviors. Here we will highlight a few of the milestones that allowed this truly integrative field of science to emerge at the intersection of disciplines such as agriculture, anatomy, biochemistry, ethology, molecular biology, physiology, and psychology.

Endocrinology

Awareness that endocrine systems played a role in behavior predates recorded history and was documented by Aristotle (c.350 BC). Anatomical and behavioral changes associated with puberty and the external location of the testes probably provided ancient humans with their first knowledge of the importance of endocrine organs. Castration as a method for inhibiting the sexual behavior of male humans or as a punishment is ancient, and testes were consumed in the search for power and virility. However, some of the earliest ideas regarding the role of the gonads in behavior were incorrect. Testicular hormones are not water soluble and beyond their nutritional benefits, ingested testes were unlikely to directly affect behavior.

With archaic roots in Chinese medicine and alchemy, modern chemistry is dated to the 18th century. During that period, pioneers such as Joseph Priestly, Carl Scheele, and Antoine Lavoisier documented the first extensive list of elements, including oxygen and hydrogen.

The idea that behaviorally active chemicals (hormones) are secreted by endocrine tissue into the blood stream and that they act on target tissues including the nervous system to influence behavior is comparatively modern. The first modern evidence of neurohormones is attributed to Otto Loewi in 1921. Loewi demonstrated that secretions from the vagus nerve ("vagusstuff") are capable of affecting heart rate. "Vagusstuff" was later identified as acetylcholine and norepinephrine. Loewi shared the Nobel Prize in 1936 with Henry Dale; Loewi and Dale are sometimes referred to as the "fathers" of neuroscience.

The formal concept of a "hormone" was described in 1905 by Ernest Starling and William Bayliss. Dale had demonstrated in the early 1900s that pituitary gland extracts (later found to contain oxytocin) could be used to induce labor, first in domestic animals and shortly thereafter in humans.

The role in endocrinology of secretions of the central nervous system can be traced to Ernst Scharrer. In 1928, Scharrer had identified the largest cells in the hypothalamus, calling these the "magnocellular neurons." In collaboration with his wife Berta, he also articulated the concept of neurosecretion. However, the behaviorally active chemicals secreted by the magnocellular neurons were not identified until Vincent du Vigneaud synthesized oxytocin in 1953 and vasopressin in 1954. Du Vigneaud received the 1955 Nobel Prize in Chemistry for the "first synthesis of a polypeptide hormone." His Nobel lecture titled "A Trail of Sulfa Research: From Insulin to Oxytocin" set the stage for the understanding that physiologically active hormones were produced not just in the pituitary or peripheral endocrine organs, but also in the nervous system (du Vigneaud, 1956).

Hormones, Behavior, and Neuroendocrine Systems

The classic tools of endocrinology arose in other disciplines, but rapidly spread to the study of behavior (Carter, 1974; Pfaff and Joels, 2017). Naturally occurring changes in behavior associated with maturation and naturally occurring pathologies were the source of many basic findings. Accidental lesions or tumors of the nervous system or endocrine abnormalities led to the earliest medical awareness of relationships between neuroendocrine systems and behavior.

The first experimental endocrine study is usually credited to A. A. Berthold. In 1849, Berthold described changes associated with removal of the testes and their reimplantation in roosters. In 1889, shortly after the invention of the hypodermic needle, an aging biologist, C.E. Brown-Sequard, injected himself with aqueous testicular extracts. Although likely the result of a placebo effect, Brown-Sequard's enthusiastic reports of renewed strength and vigor, published in the respected medical journal *Lancet*, launched the "monkey gland" era. In the decades that followed, a Viennese physiologist Eugen Steinach initiated a widely publicized series of surgical manipulations aimed at boosting endogenous hormone production and thus revitalizing aging males (Sengoopta, 2003). The "Steinach Operation" was basically a vasectomy and probably primarily based on the power of suggestion, but it attracted celebrity followers such as the poet W. B. Yeats and Sigmund Freud. Taken together, work in this period generated intense interest in the behavioral effects of "internal secretions."

Although awareness of the effects of steroids is ancient, steroid chemistry exploded only between the 1920s and 1930s with the identification and synthesis of gonadal and adrenal hormones, including testosterone, estrogen, progesterone, and glucocorticoids. Putting specific steroids into their behavioral context also began in the first half of the 20th century. For example, documentation of the rodent estrous cycle and early evidence for a role for ovarian secretions in the induction of behavioral estrus were provided in guinea pigs by Charles Stockard and George Papanicolau in 1917 and in mice by Edgar Allen and Edward Doisy in 1923. (The "pap" smear was later developed based on knowledge gained from these studies).

Initially, measurements of hormones relied on bioassays. For example, Allen and Doisy in 1923 described the use of the immature rodent uterus as a bioassay for estrogen. More advanced methods for measuring hormones, initially based primarily on radioimmunoassay, became available through the work of Rosalyn Yalow and Solomon Berson in the 1950s and 1960s, for which Yalow received a Nobel Prize in 1977. Availability of quantitative hormone assays led to a flurry of studies correlating the release of gonadal steroids with reproductive behaviors.

Once synthetic steroids were available, it was possible to show that estrogen, often in combination with progesterone, could induce female proceptivity and receptivity. Parallel studies in males focused on testicular hormones, including testosterone, and tended to concentrate on mounting behavior, considered an "appetitive behavior," or the capacity to show an erection and an ejaculatory response, sometimes called a "consummatory behavior." Much of this research originated from psychologists and anatomists, including Calvin Stone, Frank Beach, William C. Young, Daniel Lehrman, and their colleagues or students.

However, when gonadal steroids were injected, the behavioral effects tended to require hours or even days to be seen. This left open the important possibility that other chemicals, perhaps indirectly affected by steroids, could influence behavior. One of these was a small decapeptide, luteinizing-hormone releasing hormone (LHRH). The first hypothalamic releasing hormones had been identified independently in 1969 by Roger Guillemin and Andrew Schally (earning for both a share of the 1977 Nobel Prize, with Yalow). LHRH was synthesized in the hypothalamus, regulated gonadal functions of the anterior pituitary, and thus coordinated various reproductive processes including gamete production and behavior in both sexes. In 1971, two investigators (Robert Moss and Donald Pfaff) independently demonstrated that LHRH was capable of facilitating mating in female rats. These findings marked the beginning of contemporary approaches to "neuroendocrinology."

Classical approaches to mapping neuroendocrine systems include ablation of brain areas and removing tissues in which a particular compound is synthesized or where receptors are concentrated. For example, aspiration of large segments of the cortex did not prevent the expression of maternal behavior or female sexual responses, but did interfere with male sexual behavior. In contemporary behavioral endocrinology, chemicals are typically manipulated by biochemical or molecular methods, either enhancing or preventing the effects of a particular compound. In addition, new methods for mapping hormone receptors have proliferated since the 1960s. Taken together, these strategies have allowed of the analysis of underlying neural substrates and circuits for various complex behaviors including those necessary for species-typical reproductive behaviors.

Sexual Differentiation of Behavior

Differences between males and females, as well as the processes associated with sexual differentiation, have been a long-standing theme in this field. In 1916, Frank Lillie described in genetic females the development of male-like anatomical changes, known as "free-martinism," in females that had cohabitated in utero with a male sibling. This observation implicated testicular hormones in phallic development and led in time to a detailed analysis of the biology of sexual differentiation. Cross-sexual testicular transplants or gonadectomies by Steinach and others supported the hypothesis that gonadal secretions could affect anatomy and sexual behavior in later life. Experiments involving injections of testosterone in early life in guinea pigs, published in 1959 by Charles Phoenix, Robert Goy, Arnold Gerall, and William Young, were particularly influential in identifying organizational, developmental effects of hormones – in contrast to activational, short-term effects more commonly seen in adulthood (Phoenix *et al.*, 1959). (It is now known that the same molecules can have both organizational and activational consequences).

The very notion of sex differences in the nervous system remained a source of controversy for much of the 20th century, although clear evidence for sex differences in the structure of the brain and spinal cord was available in the 1960s and 1970s and was discovered to be even more strikingly apparent in the brain of a songbird (Nottebohm and Arnold, 1976). Research on sex differences focused initially on steroid-regulated processes, but recent evidence suggests that at least some sex differences in brain and behavior may be steroid-independent. Steroid-independent sexual differentiation is more apparent in some nonmammalian vertebrates such as songbirds and reptiles with temperature-dependent sexual differentiation (Sakata and Crews, 2004; Arnold, 2004).

Parental and Pairing Behavior

One of the clearest activational effects attributed to hormones is female parental behavior. In mammals, because of its association with birth, maternal behavior was logically linked to the endocrine changes of pregnancy and parturition (Pfaff and Joels, 2017). Howard Moltz, Jay Rosenblatt, and many others conducted studies mimicking the endocrine changes preceding birth. These studies implicated estrogen and progesterone (withdrawal), as well as the anterior pituitary hormone prolactin, in maternal behavior. However, even after treatment with these hormones, most reproductively naive animals still required days prior to the onset of positive reactions to infants.

Oxytocin as a candidate for the rapid induction of maternal responsiveness was initially rejected; elimination of oxytocin as a factor in maternal behavior was based on the finding that females with the pituitary gland removed (thought to be the primary source of oxytocin) remained capable of expressing maternal behavior. However, in the 1970s, it was shown that when the blood supply from maternal animals was transfused into reproductively naïve females there was an almost instant onset of maternal reactions in the naïve animals. Clearly, something was missing in the understanding of the biochemical "cocktail" for maternal behavior. Finally, in 1979, Pedersen and Prange (1979) injected oxytocin directly into the nervous system and saw a quick onset of maternal behavior in estrogen-primed, naïve females; they were also able to block maternal responses with an oxytocin antagonist, providing compelling evidence for a direct role for oxytocin in this behavior.

In studies of maternal behavior in sheep conducted in the early 1980s, Barry Keverne and his colleagues also proved that oxytocin was involved in the formation of the mother–infant bond (Carter and Keverne, 2017). Oxytocin was later shown to be released within the nervous system, confirming the fact that oxytocin could affect behavior even in the absence of its release from the pituitary gland. Oxytocin has since been implicated in the downregulation of anxiety and fear, while vasopressin and the functionally related peptide, corticotropin releasing hormone (CRH), typically have opposing effects on these processes. Generalized emotional effects of neuropeptides, mediated in part by effects on sensory systems and central and autonomic effects, probably allow mammalian females to respond appropriately to their newborn from the moment of birth. Several other social and reproductive functions have been attributed to neuropeptides. For example, studies of socially monogamous species, such as prairie voles, have revealed that both oxytocin and vasopressin are involved in pair bond formation, possibly in both sexes (Carter and Getz, 1993; Carter and Keverne, 2017). However, oxytocin, which is estrogen-dependent, may play a particularly important role in female behavior, although it is also involved in male sociality. Vasopressin, which is androgen-dependent, appears to facilitate the more active behaviors, including mate defense and territorial behaviors, which may be especially critical in males.

Diakow (1978) showed that vasotocin, an evolutionary precursor to oxytocin and vasopressin, played a role in amphibian mating behavior. Vasotocin had previously been shown to be important in egg-laying. The gene for neuropeptides related to oxytocin predates the split between invertebrates and vertebrates and it is likely that these ancient molecules have been co-opted for various "modern" functions during the course of evolution.

The Molecular Era

Methodologies arising from molecular biology are now revolutionizing our understanding of the role of specific hormones and their receptors in behavior (Pfaff and Joels, 2017). For example, research in "knock-out" mice made mutant for the gene for oxytocin, the oxytocin receptor, or the vasopressin (V1a) receptor suggests that both oxytocin and vasopressin are important for selective, social recognition learning (Young and Hammock, 2007). However, it is interesting that mice with these genetic deficits are not asocial, can still give birth, and remain capable of maternal behavior. Taken together, and in the context of studies of pair bond formation, these findings suggest that in mammals, both oxytocin and vasopressin are necessary for the development of selective social interactions. These molecules, along with many others, work as components of a highly integrated and often sexually dimorphic neural circuitry for social behavior. Molecular methods have also been used to demonstrate that differences in the expression of the genes for neuropeptide receptor are correlated with species- and individual-differences in patterns of sociality. By over-expressing certain genes, it is possible to create animals capable of showing behavioral patterns that are not usually seen in their species. For example, increasing availability of the V1a receptor in specific brain regions produces males capable of forming pair bonds, even in species, such as montane voles, for which this is atypical.

Studies of mice that lack the gene for specific steroid receptors are also providing a new understanding of the behavioral effects of compounds such as estrogen, progesterone, and androgen. This research is complicated by interactions among different hormones and the presence of various subtypes of steroid receptors. However, such work has important translational implications because of the many medical manipulations of hormones, including widely used hormone replacement therapies and contraceptives.

Recent Years: Integration and Discovery

The last few decades have seen increased integration between research on neural and hormonal mechanisms of animal behavior, as well as increased scientific integration with other subfields, for example, molecular biology, as just illustrated in the previous section. Researchers now discover social influences on the expression of genes, or use the expression of immediate early genes to identify regions of neural activity as a substitute for the brain imaging that is not yet possible in freely moving animals.

Although neuroethology and behavioral neuroendocrinology have always included an evolutionary perspective, the connection to evolutionary biology continues to produce new insights, for example, into the roles of co-evolution and sexual selection in shaping some neural and hormonal mechanisms. New approaches such as computational or network modeling of brain activity related to animal behavior are occurring through links to fields such as computer science that were not previously connected to animal behavior.

The types of behavior that have been studied physiologically show both change and continuity. There has been increased interest in animal cognition, social learning, and social relationships. At the same time, new discoveries of sensory and motor mechanisms and systems have continued to be made, for example, magnetic field detection by sea turtles and birds (leading to a search for the elusive receptors), the accessory olfactory system and its role in social behavior, and the remarkable neural system in the telencephalon of songbirds that is responsible for the perception, learning, and production of song. These last two are hormone regulated and provide excellent examples of the historical trend toward viewing neural and hormonal systems as interconnected.

References

Arnold, A.P., 2004. Sex chromosomes and brain gender. Nature Reviews Neuroscience 5, 701–708.
Bingman, V.P., 1992. The importance of comparative studies and ecological validity for understanding hippocampal structure and cognitive function. Hippocampus 2, 213–219.
Carter, C.S., 1974. Hormones and Sexual Behavior. Stroudsburg, PA: Dowden, Hutchinson & Ross.
Carter, C.S., Getz, L.L., 1993. Monogamy and the prairie vole. Scientific American 268, 100–106.
Carter, C.S., Keverne, E.B., 2017. The neurobiology of social affiliation and pair bonding. In: Pfaff, D.W., Joels, M. (Eds.), Hormones, Brain and Behavior, third ed. Oxford: Academic Press (Elsevier), pp. 117–143.
Diakow, C., 1978. Hormonal basis for breeding behavior in female frogs: Vasotocin inhibits the release call of *Rana pipiens*. Science 199, 1456–1457.
du Vigneaud, V., 1956. A trail of sulfa research: From insulin to oxytocin. Science 123, 967–974.
Eichenbaum, H., 2017. On the integration of space, time, and memory. Neuron 95, 1007–1018.
Ewert, J.P., 1980. Neuroethology: An Introduction to the Neurophysiological Foundations of Behavior. Berlin: Springer-Verlag.
Hebb, D.O., 1949. The Organization of Behavior: A Neuropsychological Theory. New York, NY: Wiley.
Hodos, W., Campbell, C.B.G., 1969. *Scala naturae*: Why there is no theory in comparative psychology. Psychological Review 76, 337–350.
Jorgenson, L.A., Newsome, W.T., Anderson, D.J., *et al.*, 2015. The BRAIN Initiative: Developing technology to catalyse neuroscience discovery. Philosophical Transactions of the Royal Society (London) B 370, pii: 20140164.
Lashley, K.S., 1963. Brain Mechanisms and Intelligence: A Quantitative Study of Injuries to the Brain; with a New Introduction by D.O. Hebb. New York, NY: Dover.
Marler, P., Hamilton III, W.J., 1966. Mechanisms of Animal Behavior. New York, NY: John Wiley & Sons.
Nottebohm, F., Arnold, A.P., 1976. Sexual dimorphism in vocal control areas of the songbird brain. Science 194, 211–213.
Pedersen, C.A., Prange Jr., A.J., 1979. Induction of maternal behavior in virgin rats after intracerebroventricular administration of oxytocin. Proceedings of the National Academy of Sciences (USA) 76, 6661–6665.
Pfaff, D., Joels, M. (Eds.), 2017. Hormones, Brain and Behavior, third ed. Oxford: Academic Press (Elsevier).
Phoenix, C.H., Goy, R.W., Gerall, A.A., Young, W.C., 1959. Organizing action of prenatally administered testosterone propionate on the tissues mediating mating behavior in the female guinea pig. Endocrinology 65, 369–382.
Reiner, A., 2005. A new avian brain nomenclature: Why, how and what. Brain Research Bullletin 66, 317–331.
Roeder, K.D., 1967. Nerve Cells and Insect Behavior. Cambridge, MA: Harvard University Press.
Sakata, J.T., Crews, D., 2004. Developmental sculpting of social phenotype and plasticity. Neuroscience and Biobehavioral Reviews 28, 95–112.
Sengoopta, C., 2003. Dr. Steinach coming to make old young!: Sex glands, vasectomy and the quest for rejuvenation in the roaring twenties. Endeavor 27, 22–126.
Sherry, D.F., 1997. Cross-species comparisons. Ciba Foundation Symposia 208, 181–189.
Stellar, E., 1954. The physiology of motivation. Psychological Review 61, 5–22.
Striedter, G., 2005. Principles of Brain Evolution. Sunderland, MA: Sinauer.
Washburn, M.F., 1936. The Animal Mind: A Text-book of Comparative Psychology, fourth ed. New York, NY: The Macmillan Company.
Wilson, E.O., 1998. Consilience: The Unity of Knowledge. New York, NY: Vintage Books, Random House.
Young, L.J., Hammock, E.A., 2007. On switches and knobs, microsatellites and monogamy. Trends in Genetics 23, 209–212.
Zupanc, G.K.H., 2004. Behavioral Neurobiology: An Integrative Approach. Oxford, UK: Oxford University Press.