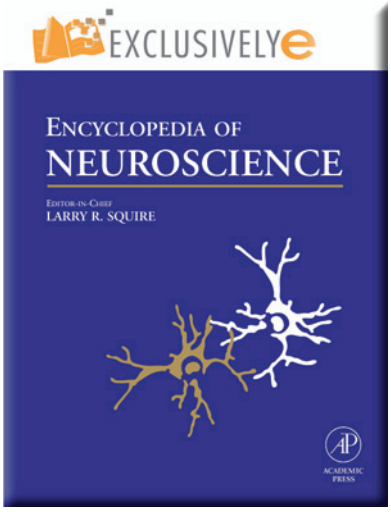

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Hormones and Behavior

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Introduction

There are some stimuli encountered by animals to which the most appropriate response is invariant. If a large predator appears, seeking refuge almost always benefits a foraging rodent. Then there are other stimuli and situations to which the most appropriate response is dependent on the internal state of the individual. A hungry animal, for example, may consume food that a well-fed animal would ignore. There are many such internal or physiological variables that influence animals' behavior, and some change rapidly, whereas others change more slowly. Using the example of feeding, in addition to the difference in behavior between an animal that has just fed and an animal that has not fed for several hours, two animals with equally full stomachs may behave differently if one is fat and the other is lean. Furthermore, some of these physiological factors change unpredictably, whereas others change cyclically across a range of timescales from minutes to years. Such cyclic variability is typical of the reproductive states of many animals – for example, the ovarian cycle of most vertebrates.

For many of these phenomena, changes in a particular physiological parameter are associated with changes in the levels of one or more signaling molecules produced by the body. For several kinds of behavior, described in this article, it has been possible to show that a particular signaling molecule or hormone is the critical agent inducing the behavior appropriate for the physiological state associated with that hormone. Hormones, in other words, can be thought of as messengers that inform the brain of the state of the rest of the organism and enable the appropriate behavior. This article presents an overview of current knowledge about the relationships between environment, hormones, and the brain. Then, for three particular kinds of behavior (i.e., copulatory behavior, affiliative behavior, and feeding behavior) it describes in more detail the endocrine and neural systems that are thought to underlie these relationships.

Research

To say that a hormone influences a behavior is to say that an organism in one hormonal state responds to a given stimulus with one response, whereas the same organism in a different hormonal state exhibits a different response to the same stimulus. The elucidation of this relationship involves the following questions:

- What are the hormonal states involved, in terms of chemical identity, concentrations, and timing of hormonal exposure?
- What is the stimulus?
- What are the alternative behavioral responses?
- Which cells in the nervous system are involved in conveying information about the stimulus to the effectors that mediate the responses?
- On which of these cells does the hormone(s) have its effect?
- What kinds of receptors in these cells bind the hormone?
- Following hormone receptor binding, what kinds of changes occur in each cell, in terms of second-messenger activation, gene expression, and so on?
- How do these changes in each cell produce changes in cell-to-cell neurotransmission so that the stimulus–response relationship is altered?

Hormones

Historically, for a substance to be considered a hormone, it had to satisfy three criteria: synthesis by a specified kind of cell or tissue, release into and transport by the blood, and action on a specified target cell or tissue type(s). With increasing appreciation of physiological signaling systems, the second of these criteria has been become more complicated, and a system of adjectives has been developed to describe signaling molecules that act at various distances. Molecules that act within the cell that produces them are called intracrine signals, those that are secreted but act on the secreting cell are called autocrine, and those that act on adjacent cells are called paracrine. This article deals principally with endocrine systems – that is, those involving signaling molecules secreted from the producing cell into the intracellular fluid and exerting a physiological effect on other cells. However, several kinds of signaling molecules satisfy this definition that are not thought of as hormones. In particular, signaling molecules such as dopamine that are released by neurons and influence large numbers of other neurons are known as neuromodulators and not as hormones. Furthermore, some substances such as the cytokines modulate interactions between various components of the immune system and satisfy all three criteria perfectly well but are not called hormones, perhaps because

they are the historical purview of immunologists rather than endocrinologists.

Most of the well-studied hormones belong to one of four chemical classes, and as a result of their biochemical properties, members of a particular class tend to serve similar functions and engage similar transduction machinery in their target cells.

Steroids

Steroids, such as the gonadal hormones estrogen, progesterone, and testosterone, and the adrenal steroids corticosterone and aldosterone are synthesized from cholesterol and have a four-ring structure similar to the estrogen molecule shown in Figure 1. Their hydrocarbon-dominated structure makes their solubility in water low and that in lipids high. Consequently, they pass easily though cell membranes, and a steroid secreted in one part of the body will gain access to all tissues. The concentration of hormone reaching target tissues, however, is limited by the low carrying capacity of the blood, although for many steroids, this is augmented by specialized carrying proteins. Many of the effects of steroid hormones on behavior are mediated by proteins belonging to the nuclear receptor family that dimerize on binding ligand and then associate with the DNA of regulatory regions of genes to influence gene transcription. There is also accumulating evidence that steroids sometimes interact with membrane-associated receptors, and such effects are generally more rapid than the hours or days during which the nuclear receptors manifest their influence.

Prostaglandins

Prostaglandins are signaling molecules derived from fatty acids and are common mediators of physiological processes. Evidence of direct involvement in vertebrate behavioral regulation is not abundant, but, for example, prostaglandin E has been implicated as a key component of the developmental process of masculinization of the brain and subsequent behavior.

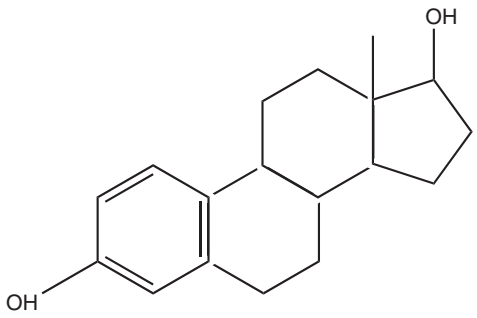

Figure 1 17β estradiol. Estradiol and other sex steroids share the basic structure of three six-carbon rings and one five-carbon ring, and they are interconverted by modifications of the substituent groups. Estradiol, for example, is formed from testosterone by the aromatization of the first six-carbon ring and the reduction of the ketone group on this ring to the hydroxyl shown here.

Monoamines

Monoamines, such as epinephrine, serotonin, and melatonin, are small molecules derived from single amino acids. They generally exert their effects through membrane-bound receptors with an extracellular ligand-binding site, often a G-protein-coupled receptor (GPCR), whose action on ligand binding is often to influence the production of a second messengers such as cyclic AMP.

Peptides

Peptide hormones are polymers of small numbers of amino acids (from fewer than ten to a few hundred); in other words, they are small proteins. Like monoamines, they generally utilize membrane-bound receptors, often GPCRs. The complexity of peptide hormones means that they often show variation in exact structure according to the organism examined. Steroids and monoamines are chemically identical from species to species (e.g., testosterone in a fish is identical in structure to testosterone in a human), although there are species differences in the nature and pattern of synthesis and release of the hormone (e.g., in many male fish 11-ketotestosterone is the dominant circulating androgen and is produced by steroidogenic enzymes not present in humans).

Behaviors Influenced by Hormones

Sexual Behaviors

There are three very important roles for hormones in modulating reproductive behavior. First, males and females have different roles in reproduction, and gonadal sex steroids tell the brain whether male-typical or female-typical behavior is appropriate. Second, animals do not reproduce throughout their lives but, rather, have a reproductively quiescent period before puberty, and, according to the species, sometimes breeding and nonbreeding seasons; hormones serve to encode reproductive status of the animal. Third, in females, sexual behavior is often restricted to narrow windows of the ovarian cycle, which are also associated with particular hormonal states. In general, testicular androgens enable the expression of male-typical behaviors such as competitive aggression, mounting, and intromission, whereas ovarian hormones, particularly estrogen, enable the display of female-typical sexual behaviors such as estrous and maternal behaviors. However, the hormones do not

act as simple on/off switches but, rather, are players in a complicated program of interaction between the developing animal and the environment, acting at multiple time points in both the brain and the periphery to coordinate the critical function of reproduction.

Development A central concept in the behavioral neuroendocrinology of reproduction is the organization–activation hypothesis. This idea was originally formulated to describe the development of the peripheral reproductive organs. Mammalian embryos are initially bipotential, possessing gonadal and genital primordia of both sexes. Working with rabbit embryos *in utero* in the 1940s and early 1950s, Alfred Jost recognized that early in development, castration of a male embryo would result in the development of the female-appropriate genital tract and the disintegration of the male genital tract, whereas a similar operation on an embryonic female did not affect the development of the female genital primordia or the disintegration of the male genital tract. This organization (i.e., the irreversible selection of which sexual structures are retained and which are lost) is irreversible and is restricted to a critical developmental time period. Later, once puberty occurs and levels of sex steroids increase again, the sexual structures develop further from their prepubescent state to their reproductively functional state. This activation of the previously organized structures is generally reversible, and in seasonally breeding animals it is commonly executed and reversed each breeding season.

Experiments conducted by William C Young's group in the 1950s suggested that the same kind of relationship between embryonic and adult effects of hormones might hold in the brain. Female guinea pigs that had been exposed to androgens *in utero* were much more likely to express male-like copulatory behavior when exposed to androgens as adults, and they were also less likely to express female-typical receptive behavior when treated with estrogen and progesterone. These two effects of prenatal androgenization, known as masculinization and defeminization, together constitute the process of behavioral organization and are experimentally separable by the timing of the critical developmental window and the nature of the hormones involved. During normal development, it appears that both components are mediated by circulating testosterone, although according to the species involved, the local conversion (i.e., at the site of action in the brain) of testosterone to estrogen, or aromatization, may be more or less critical. In rats, for example, administering an aromatase inhibitor prenatally can block masculinization. A schematic depiction of the development of sexual dimorphisms in anatomy, physiology, and behavior related to reproduction is presented in Figure 2. In addition to the behavioral motor patterns of copulation, such as female-typical receptivity and male mounting and intromission, other aspects of sexually dimorphic behavior can be subject to the organizational effects of embryonic hormone exposure. Examples include sex-typical play patterns, aggressiveness, and adult preference for sexual partners of the opposite sex.

Site of action It is presumably not a coincidence that the same hormones that control the development of reproductive organs also control the expression of behaviors utilizing those organs. In vertebrates of both sexes, the gonadal steroids that regulate the production of gametes also enable mating behavior, a kind of pleiotropy with obvious adaptive significance. More subtly, a given hormone will often have many sites of action within the brain for two reasons. First, expression of one kind of behavior may be associated with suppression of another kind of behavior. For example, the rise in progesterone associated with early pregnancy in female rabbits not only induces nest-building behavior but also suppresses mating behavior. Second, behavioral responses involve many different areas of the brain. A large number of experiments have identified specific nuclei of the limbic forebrain to be critically involved in the display of sexual behavior. Furthermore, various methods reveal these to be reciprocally interconnected, to contain sex steroid hormone receptors, and to be sexually dimorphic in their volume and synaptic organization as a consequence of the nature and frequency of sex steroid hormones secreted perinatally. Importantly, these properties appear to be evolutionarily conserved. Furthermore, these limbic nuclei form integrated circuits that are sensitive to both somatosensory and hormonal stimuli with overlapping functions that subserve all sex steroid hormone-modulated social and reproductive behaviors. In this manner, social and reproductive behaviors emerge from the activity of a unitary neuroanatomical framework rather than being the product of activity of a single brain area.

Interaction with the environment With increases in our understanding of the genetic determination of gonadal sex, it is becoming possible to map out, albeit with gaps, a pathway from the sex chromosomes an individual inherits, through the development of gonads, the secretion of sex-typical patterns of hormones, the sex-typical development of the brain, to the expression of sex-typical behavior. However, an individual vertebrate is not a hormone-driven automaton, blindly executing whatever behavioral program its gonads dictate, any more than the shape of its

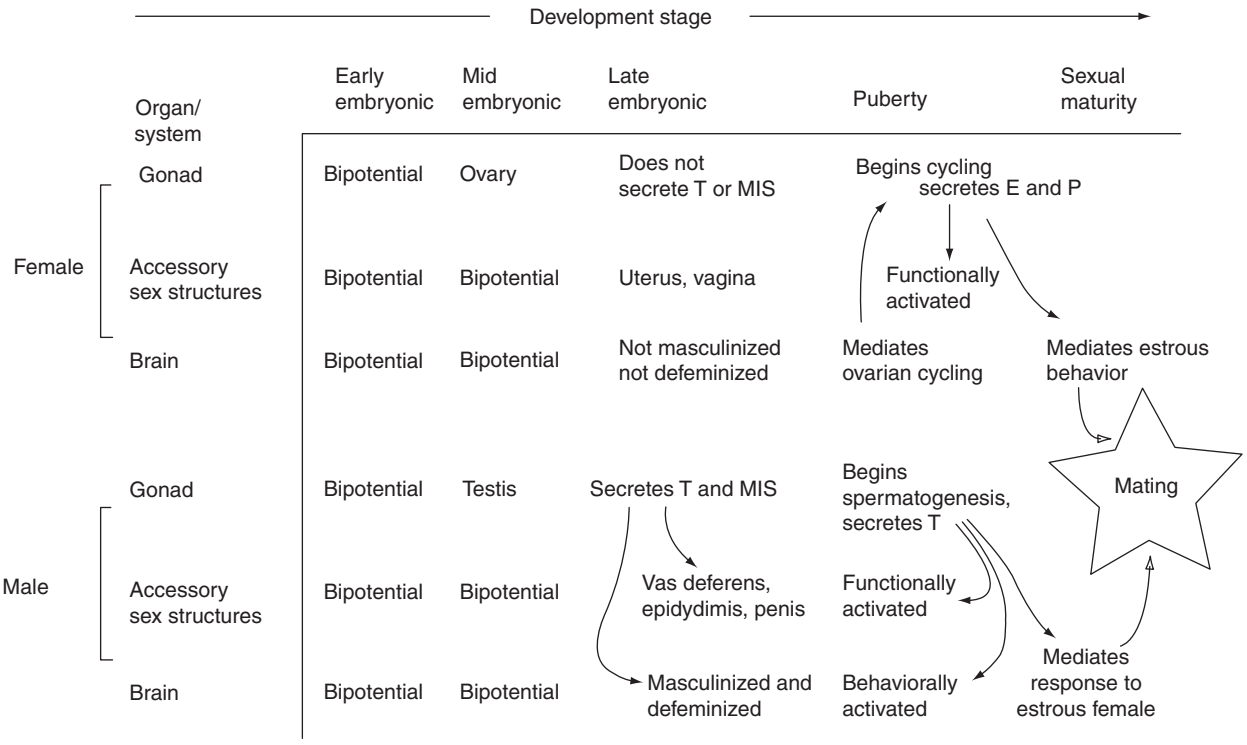

Figure 2 Sex steroids act in various ways throughout development to coordinate physiology and behavior. This figure is a schematic depiction of important events in the development of female and male mammals, illustrating the interaction between the three organ systems (gonad, peripheral sex organs, and brain) and ultimately between the two sexes. In mammals, the sex is fixed at conception, and a molecular cascade will determine the sexual fate of the gonad. Secretions of the fetal gonad are then principally responsible for determining the sexual phenotype of the other two systems. This includes the accessory sex structures where testosterone maintains the Wolffian duct and enables them to develop into the epididymis and vas deferens, whereas Müllerian inhibiting substance (MIS), a protein signaling molecule secreted by the testis, induces the disintegration of the Müllerian ducts, which otherwise (i.e., in the developing female) develop into the uterus, cervix, and parts of the vagina. Fetal testosterone is also responsible for masculinizing (i.e., enabling future masculine) and defeminizing (i.e., disabling future feminine) behavior by its actions on the developing brain. At puberty, the body and brain thus organized during fetal development are activated by increasing levels of sex hormones, and animals of either sex become physiologically capable of reproduction and behaviorally able to mate. Arrows signify the actions of secreted molecules. E, estrogen; P, progesterone; T, testosterone.

development is determined entirely by its genome. Rather, each individual develops and behaves in continual interaction with other individuals and with other aspects of its environment. Such environmental influences on the development of the hormone–behavior relationship include hormone exposure *in utero* from mother and siblings, postnatal interaction with mother and siblings, the type and availability of food, and sexual and aggressive interactions with other individuals in adulthood, all of which can act to increase, decrease, or qualitatively change the expression of sex-typical as well as sex-atypical behaviors.

Copulatory behavior Mammalian male sexual behavior is dependent on testicular androgens so that castration eliminates the behavior in the majority of individuals, and administration of exogenous testosterone will reinstate it. In naturalistic settings, the expression of male sexual behavior is generally determined by the sexual behavior of females. Female sexual behavior is largely under the control of ovarian steroids and is therefore tightly linked to the ovarian cycle, of which a schematic is presented in Figure 3. In the rat, the cycle is usually 4 days long, with estrogen levels rising continuously until ovulation on the afternoon of the fourth day and then falling back to baseline, whereas progesterone levels remain low except on the day of ovulation. The periovulatory increase in progesterone following a period of sustained estrogen exposure is the hormonal antecedent to behavioral estrus, including increased attractivity, receptivity, and proceptivity, and can be mimicked in ovariectomized rats by an injection of estrogen, followed 48 h later by an injection of progesterone. In the wild, this cycle is unlikely to persist for long since behavioral estrus will normally involve mating and pregnancy, and the sustained high levels of progesterone

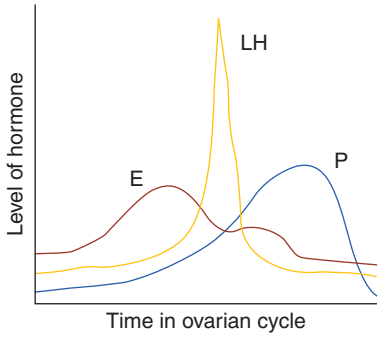

Figure 3 Hormonal changes across the ovarian cycle. Levels of three hormones are shown, scaled arbitrarily on the vertical axis and plotted against the time of the ovarian cycle. The horizontal axis would thus represent 4 days for a rat, or 28 days for a human. Luteinizing hormone (LH) is shown because it is a reliable marker of ovulation, rather than for its behavioral importance. In rodents, the rise in estrogen (E) levels before ovulation followed by a rise in progesterone (P) levels are critical determinants of estrous behavior.

originating from the corpora lutea suppress further ovarian cycles until gestation is complete. Other species have cycles of different lengths, but the general pattern of estrogen levels rising gradually before ovulation and then progesterone levels rising during and after ovulation is conserved. There are also some species such as cats, in which there is no regular ovarian cycle but, rather, ovulation is induced by copulation.

In 1976, Frank A Beach proposed that the sexual behavior of female mammals could generally be thought of as including three components, namely attractivity, proceptivity, and receptivity. The attractivity of a female (many aspects of which are obviously nonbehavioral) represents the degree to which a male will seek and elicit copulation with her. Proceptivity is the degree to which she will actively seek out a sexual partner and attempt to initiate copulation. Receptivity is the degree to which a female will allow the courtship and intromission of a male that attempts to copulate with her. These three components are still extremely useful heuristically in describing the copulatory sequence of mammals.

In rats, attractivity is assessed largely through olfactory and pheromonal cues (Figure 4(a)). Little is known about the neural mechanisms by which females assess a male's value as a mate, but the neuroanatomy underlying male processing of female pheromonal signals is known in some detail (Figure 5(a)). Volatile odorants are detected at the olfactory epithelium and larger, less volatile pheromones by the vomeronasal organ. These sensory structures project respectively to the main and accessory olfactory bulbs and then via the amygdala (particularly medial division) and the bed nucleus of the stria terminalis to the medial preoptic area (MPOA). The MPOA plays a particularly important role in integrating male-typical copulatory behavior, especially the hormonal gating thereof. Although prolonged systemic exposure to androgens is necessary for the development of sexual structures such as the penis, it seems that expression of copulatory behavior as an adult is simply determined by exposure of a small number of brain areas to hormone, particularly the MPOA.

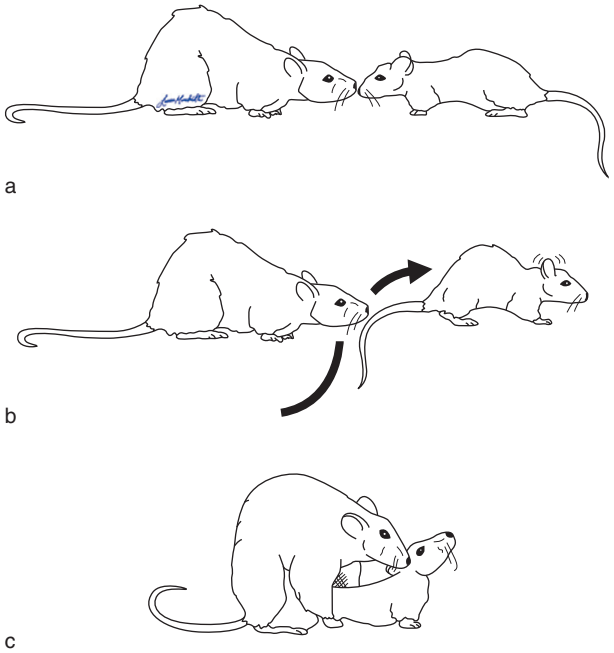

Figure 4 Characteristic behaviors in the rat mating sequence. Rat social interactions of all kinds, including sexual, often involve mutual olfactory examination, particularly of the facial area (a). When the interaction involves an estrous female and a suitable mate, she will express a suite of proceptive behaviors that signal her sexual status to the male, including rapid approach and withdrawal, hopping and darting, and rapidly moving her ears (b). A sexually active male will follow and mount her (c). If receptive, she will express the flattened posture of lordosis, with head and rump elevated and back depressed, enabling him to intromit, thrust, and ejaculate. Illustrations by Lauren Munchrath.

An estrous female will solicit the male's attention with proceptive behaviors such as approaching him and rapidly withdrawing with a characteristic dart-hopping movement, ear wiggling, and other behaviors (Figure 4(b)). Comparatively little effort has been made to elucidate the neuroanatomical substrates of this behavior as distinct from those subserving the receptive behavior that follows.

A sexually active male will follow a proceptive female and attempt to mount her. The stimulation from his snout and forepaws on her rump and flank induces the estrogen- and progesterone-dependent reflexive receptive posture known as lordosis shown in Figure 4(c), and whose neural substrates are schematized in Figure 5(b). The essential reflex arc flows

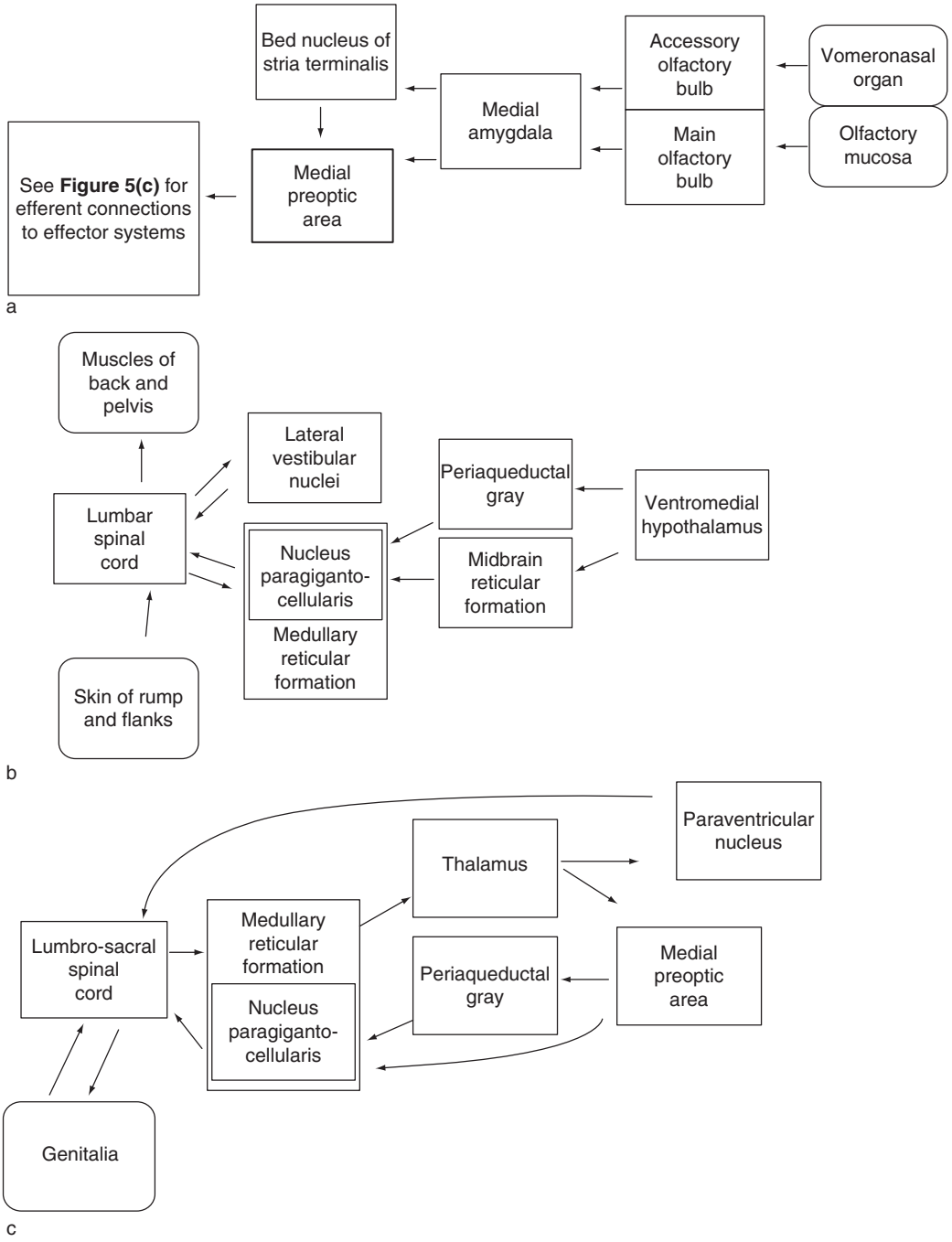

Figure 5 Neuroanatomical pathways mediating copulatory behavior. Brain nuclei known to be important in the expression of the various behaviors are depicted as square boxes, and the projections between them (of which some are excitatory and some inhibitory) are shown as arrows. Sensory and effector organs are shown as rounded boxes. Brain nuclei critical for hormonal control over behavior are shown as bold boxes. The neuroanatomy involved in processing sexually relevant chemosensory information has been well studied in the male rodent (a) and involves the pathway from the main and accessory olfactory bulbs to the amygdala, particularly the medial division, and thence via the bed nucleus of the stria terminalis and an alternative route via the ventral amygdalofugal pathway to the medial preoptic area. Exactly what happens to this information once it reaches the medial preoptic area is unknown, but it is presumed to result in the decision to attempt to mount. Once the mount is established, events in both the female and the male involve reflex arcs mediated by well-characterized neural circuits, shown by bold arrows. (b) Lordosis in the female involves the transfer of sensory information from the male's mounting and thrusting movements to the lumbar spinal cord, whence it ascends to the brain stem motor nuclei responsible for integrating the muscular motor pattern of lordosis. Descending control over this reflex arc is exerted by the ventromedial hypothalamus via the periaqueductal gray and the midbrain reticular formation. The medial preoptic area plays an inhibitory role. (c) Erection and ejaculation in the male are spinal reflexes, albeit subject to descending influences from higher in the brain, whereas other motor patterns of male-typical copulation are mediated by brain stem motor areas. The periaqueductal gray exerts an inhibitory influence on these lower copulatory reflexes, and a major role played by the medial preoptic area is probably disinhibition achieved by inhibiting the periaqueductal gray.

from the sensory receptors on the skin via the pudendal nerve to the lumbar spinal cord. Then it is relayed to the brain stem motor centers of the lateral vestibular nuclei and the nucleus paragigantocellularis of the medullary reticular formation. These motor centers project back to the lumbar spine and orchestrate the motor pattern of lordosis via their control over the musculature of back and pelvis. Hormonal control of this behavior is achieved by higher centers in the brain, particularly the ventromedial hypothalamus, which influences the nucleus paragigantocellularis via the periaqueductal gray. A similar system of nuclei mediates the motor and other physiological responses of the mounting male (Figures 4(c) and 5(c)). Sensory information from the penis is relayed via the pudendal nerve to the sacral and lumbar spinal cord. Some important components of the male sexual response, such as erection and ejaculation, are spinal reflexes and are observed even in rats spinally transected above the thoracic level. Sensory information, however, is conveyed to the medullary reticular formation, whose nucleus paragigantocellularis integrates reflexive motor patterns such as thrusting, and then via the thalamus to higher areas in the brain. Descending signals from the MPOA reach the nucleus paragigantocellularis directly or via the periaqueductal gray. Other aspects of female sexual behavior, such as mate choice, the rewarding properties of copulation in various different contexts, copulation for other reasons than reproduction, and an individual's preference for one particular mate over others, are also beginning to be studied.

Aggression The ecology of sexual aggression is complex, with a number of factors influencing which individuals are aggressive to which others under which circumstances in which species. This complexity in the nature of the behavior is reflected in the relationship between the behavior and its hormonal antecedents, and general principles are difficult to extract. However, with respect to the endocrinology of male reproductive aggression, observations from a number of species can be reconciled in a conceptual framework known as the 'challenge hypothesis,' originally elaborated by John Wingfield and colleagues to explain some of the available observations concerning testosterone and aggression in songbirds. This hypothesis posits that testosterone levels are low during nonreproductive periods, rise to intermediate levels during breeding to support reproductive physiology such as spermatogenesis and copulatory behavior, and increase to especially high levels during periods characterized by frequent agonistic interactions with other males, sometimes apparently as a result of such agonistic interactions.

Again, possibly because of the complexity of the phenomenon, the neuroanatomical substrates of aggression have been less thoroughly elucidated than those subserving copulatory behavior, but some kinds of aggression seem to involve the lateral septum and the nucleus accumbens, in addition to the amygdala and various subdivisions of the hypothalamus. These areas express androgen and/or estrogen receptors and also various types of serotonin receptor. Serotonin appears to occupy a central role in the control of aggressive behavior, with reduced levels of serotonin receptor activation being associated with increased aggressiveness in a range of contexts in a range of species. This is not a completely valid generalization, however, since maternal aggression is associated with increased serotonin levels.

Parental behavior Parental behavior obviously includes both maternal and paternal behaviors, but since paternal behavior is not common other than in birds and certain fish taxa, this discussion is largely limited to females. Once again, rats have been the main focus of research, and important kinds of maternal behavior in this species include nest building, licking and grooming, nursing, pup retrieval, and maternal aggression. These behaviors are exhibited at different points in the reproductive cycle (or at least exhibited at different frequencies), and their expression is partly dependent on the endocrine events associated with pregnancy, lactation, and birth. The end of pregnancy is characterized in rats by high estrogen levels, plunging progesterone levels, and a sharp spike in prolactin levels, whereas the event of parturition is associated with a peak of oxytocin secretion. All of these hormonal parameters appear to be involved in the onset of maternal behavior. Expression and maintenance of the behavior is not only partly controlled by hormones but also largely dependent on stimulation from the young so that nursing female rodents are not exceptionally aggressive except in the presence of their pups.

Pair bonding In some species, males and females form stable reproductive pairs in order to raise young. Oddly, the neuroendocrine mechanisms underlying this behavioral phenomenon have received little attention in birds, in which the behavioral pattern is common, and instead have been most extensively investigated in microtine rodents. These studies have implicated corticosteroids and the peptide hormones oxytocin and vasopressin in mediating pair-bond formation in these animals. In the prairie vole, socially naive animals will form monogamous pairs with the partners with whom they first mate. The genesis of this pair bond is

dependent on copulation-induced oxytocin release in females and on a combination of vasopressin and corticosterone in males.

Other Hormonally Influenced Behavior

Feeding is important, but there are times, such as when an animal has a full stomach, that it is inappropriate or, when the animal is fat, that it is less important than other activities such as reproduction. Accordingly, vertebrates have evolved a network of signaling systems that keeps the brain informed about the animal's short-term and long-term state of nutrition and enables appropriate feeding behavior. In addition to direct neural pathways to the brain, the gastrointestinal tract produces a range of peptide hormones that encode information about the quantity and quality of food being ingested and processed. The majority of these hormones, such as cholecystokinin and glucagon-like peptide 1, appear to be satiety inducing, rising after feeding and reducing food intake when administered exogenously. An interesting exception is ghrelin, which appears to peak before (i.e., in anticipation of) feeding and increases food intake. Just as other behaviorally important hormones often mediate nonbehavioral aspects of the processes with which they are associated, these gastrointestinal peptides are intricately involved in the regulation of gut function in addition to their role in regulating feeding behavior.

In the longer term, the brain receives information about nutritional status via adiposity signals such as leptin secreted by adipocytes and insulin from the pancreas. In the central nervous system, the arcuate nucleus appears to play a central role in regulating feeding via projections to the lateral, paraventricular, and ventromedial nuclei of the hypothalamus. The various peripherally generated nutrition-related signaling molecules reach the arcuate nucleus via the median eminence and are transduced into two kinds of signals – either suppressing food intake and involving the expression of pro-opiomelanocortin and cocaine- and amphetamine-related transcript or augmenting food intake and involving the expression of neuropeptide Y and agouti-related peptide.

It is important to recognize the degree to which separate hormone–behavior systems are interrelated. For example, in some species (e.g., elephant seals), males do not feed during the mating season, and in most species the onset of puberty is dependent on nutritional status.

Summary

Several kinds of behavior are dependent on or influenced by circulating hormones. Many, but not all, of these are related to reproduction and are accordingly influenced by the same suite of steroid and peptide hormones that serve to regulate the other aspects of reproductive physiology. Sex differences in vertebrate hormone metabolism occur throughout the development of the individual, from the differentiation of the fetal gonad until death. For much of this period, these hormonal differences have effects, both subtle and profound, on the brain and on behavior. In many cases, the systemic hormonal antecedents to particular behaviors in adults are well known, although in the brain, the localized release of various peptide hormones and the localized metabolism of steroids make it a much more difficult task to identify which hormone is contributing how much to which effect in which target cell. For some behaviors, particularly those such as rodent lordosis in which the stimulus–response relationship is a simple one, the anatomy of the neural circuits responsible for responding transducing hormone–behavior relationships is fairly thoroughly elucidated. In others, such as female proceptive behaviors, the neural substrates are more of a mystery. In almost all cases, our knowledge of neural structure stops at the level of anatomical connectivity. Despite the fact that the first sex difference in neural structure was reported at the ultrastructural level, we still know very little about how hormones alter the flow of information from one neuron to another, which is presumably a prerequisite for changing behavior. This last lacuna in our knowledge of hormone–behavior relationships is perhaps the most inevitable, given that the same problem exists throughout behavioral neuroscience, and for the same reason it is one of the most challenging.

See also: Aggression: Hormonal Basis; Development of Behavior; Emotional Hormones and Memory Modulation; Estrus and Menstrual Cycles: Neuroendocrine Control; Gene Expression Regulation: Steroid Hormone Effects; Gonadal Steroid Actions on Brain; Hormonal Signaling to the Brain for the Control of Feeding/Energy Balance; Hormones and Memory; Neuroendocrinology of Social/Affiliative Behavior; Sexual Behavior: Neuroendocrine Control.

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