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# Handbook of Neurochemistry and Molecular Neurobiology

*3rd Edition*

## Behavioral Neurochemistry and Neuroendocrinology

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Abel Lajtha(Ed.)

# Handbook of Neurochemistry and Molecular Neurobiology

## Behavioral Neurochemistry, Neuroendocrinology and Molecular Neurobiology

Volume Editor: Jeff Blaustein

With 130 Figures and 7 Tables

Springer

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# Preface

Behavioral neuroscience was not covered extensively in the second edition of the Handbook of Neurochemistry, published in 1983. That was nearly a decade before the formation of the international society, which named itself after this discipline, the International Society for Behavioral Neuroscience, and it was even longer before the inception of the Society for Behavioral Neuroendocrinology, which focuses on a subfield of behavioral neuroscience. The progress that has been made in the study of the cellular and molecular underpinnings of behavior was almost unimaginable in 1983. The field has prospered thanks to development in novel drugs, genetic models, and related molecular techniques, neuroanatomical techniques, including *in situ* hybridization histochemistry, new immunocytochemical techniques, real time PCR, microarrays, and more sophisticated behavioral analysis.

This volume is filled with a tremendous amount of history that documents the coming of age of behavioral neuroscience. Learning the history and following the development of a field are often an important part of understanding an area of science, and many of the authors have elaborated extensively on the history of their field. Though behavioral neuroscience has advanced tremendously in recent years, impediments to progress still remain in this field. For example, behavior still occasionally takes a back seat to the study of simpler physiological endpoints, such as the control of ovulation. Yet, it is the more complex regulation of behavior and the interactions of the environment on it that allow for fertilization, without which, ovulation would be irrelevant. In his memorable biography of the field of hormones and behavior, Frank Beach (1981) explained some of the background for bias against studies of behavior. He also provided what is perhaps one of the most noteworthy examples of this bias against studying behavioral endpoints. In 1935, Edward Dempsey, working in William C. Young's group, made the heretic proposal that sequential exposure to estradiol and progesterone was necessary to induce the expression of estrous behaviors in female guinea pigs. This made no sense at the time since it was widely believed that the source of progesterone was the corpus luteum, most definitely formed after ovulation, long after the animal's estrous behavior had commenced. Beach recounts that Edgar Allen, a co-discoverer of estradiol, suggested that Young would be "well-advised to give up behavior and return to his more promising early studies on physiology of the epididymis." It was to be another 30 years before novel biochemical procedures would be developed, which would prove Dempsey, Young and colleagues correct; progesterone was being secreted from another source before the formation of the corpus luteum. Behavioral studies had indeed informed physiology.

Throughout this volume, you will find examples of dogmas that ultimately did not hold water (the timing of progesterone secretion during the estrous cycle just discussed is but one example). Time and time again, throughout the history of science, scientists who have questioned dogma have been subjected to ridicule or derision for their actions. Win or lose, the dogma fight is always worth waging, and it is good science. If the dogma represents truth, it will stand; if not, it will eventually topple, but usually not without significant battle. I dedicate this volume to all scientists who have at one point or another challenged dogma in their work.

In this volume, I have collected in one place the expertise of numerous authorities in the diverse field of behavioral neuroscience. A volume of this size does not allow for an exhaustive treatment of the neurochemistry, neuroendocrinology, and molecular neurobiology of behavior; rather it is a sampling of some fascinating areas within the realm of behavioral neuroscience. Moreover, because of my personal bias, these

areas of behavioral neuroscience often have an important, well-developed, endocrine slant. To appreciate how much space a comprehensive treatment of the entire field would require, consider that a comprehensive coverage of the subfield, the relatively narrow field of behavioral neuroendocrinology, was recently accomplished admirably in a discipline-defining, five-volume, and nearly 4,000 page work, which was edited by Donald W. Pfaff et al.

It is impossible to acknowledge here each of the authors and all of the important findings of the fields that they represent. Suffice it to say that tremendous progress has been made in the study of reproductive behaviors, affiliative and aggressive behaviors, bird song, sex differences, the hypothalamo-pituitary-adrenal axis, stress, ingestive behaviors, fear, cognitive function, reward, rhythms, and sleep. The book starts at the beginning with reproduction and ends appropriately with sleep. Between those two basic, life-generating and restorative activities, tremendous progress in all of these fields is described.

Recent changes in the funding climate have affected many areas within behavioral sciences. For example, the National Institutes of Health have shifted emphasis to more translational research; in some cases, at the expense of more basic research. This volume is filled with examples of basic research that have led to a better understanding of the human brain and behavior. I hope that it serves as testament to the indispensable value of basic research, as well as translational research, in behavioral neuroscience.

Frank Beach ended his biography of the field of behavioral endocrinology with the following passage: "Scientists with doctorates in psychology study development of progesterone receptors in neurons of the rat hypothalamus while other investigators initially trained in pharmacology invent elegant behavioral measures of sexual motivation in the estrous female. These developments appear to represent more than a mere borrowing of techniques by one discipline from another. Instead they seem to reflect progress toward recognition of common goals and shared theoretical interests. If such indeed is the case, behavioral endocrinology may well be a discipline *in statu nascendi*," that is, a discipline in a state of being born. He could have said the same about behavioral neuroscience. I submit that the discipline of behavioral neuroscience has become a fully developed discipline with investigators answering questions that truly run the gamut from molecular to behavioral and all levels in between.

I am immensely grateful to all who contributed to this volume. Writing a comprehensive review of a field, even one's specialty, is time-consuming and laborious, and it invariably takes time away from other worthy tasks. My job of convincing colleagues to contribute to this volume was made relatively easy because previous versions of the Handbook of Neurochemistry have been well received, and have often served as landmark volumes in their respective fields. It is my hope that the authors will be well compensated for their work with the satisfaction of knowing that their reviews will be read and that, as their areas evolve, progress can be updated and followed in the electronic version of the Handbook.

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April 2006

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# 1 Neuroendocrinology of Male Reproductive Behavior

*M. J. Baum*

**Abstract:** Berthold, working in the mid-nineteenth century, first published data linking the endocrine secretions of the rooster testes to the display of masculine courtship behavior. Since then hundreds of experiments have been published showing that testosterone is the endocrine signal produced by the Leydig cells of the testes, which in male mammals contributes both to the activation of mating behavior in adulthood and to the organization during perinatal life of neural mechanisms that control this behavior. The broader topic of the neural basis of male sex behavior has recently been reviewed (Hull et al., 2002). Therefore, the present review will concentrate selectively on neuroendocrine variables that control the adult activation as well as the perinatal development of brain mechanisms controlling male-typical sexual motivation, courtship, penile erection, and coital behaviors, with an emphasis on common mammalian models including the rat, mouse, hamster, ferret, and monkey. A common theme to all of these studies is that testosterone exerts its actions in the neural systems controlling male-typical sexual behavior both by acting directly via neural androgen receptors and after neural aromatization to estradiol or 5α–reduction to dihydrotestosterone. Estradiol, in turn, affects neural morphology and function via estradiol receptors of the alpha- or beta-subtypes, whereas dihydrotestosterone, like testosterone, acts via androgen receptors. The evidence reviewed indicates that there are many similarities and a few differences among mammalian species, including higher primates, in the principles of neuroendocrine regulation that control the development and expression of male sexual behavior.

**List of Abbreviations:** AOB, accessory olfactory bulb; AR, androgen receptor; ArKO, aromatase knockout (mouse); ATD, 1,4,6-androstatriene-3,17-dione (aromatase blocker); BNST, bed nucleus of the stria terminalis; CA, cyproterone acetate; CBP, cAMP response element binding protein; COX-2, cyclooxygenase 2; CPP, conditioned place preference; DA, dopamine; DHT, dihydrotestosterone; DHTP, dihydrotestosterone propionate; DNA, deoxyribonucleic acid; DOPAC, 3,4-dihydroxy-phenylacetic acid; E, estradiol; E25, embryonic day 25; EB, estradiol benzoate; ER, estrogen receptor; F1, first generation; GABA, gamma amino butyric acid; GnRH, gonadotrophin releasing hormone; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; INA-3, third interstitial nucleus of the anterior hypothalamus; IR, immunoreactivity; LS, lumbar spinal cord; MeA, anterior amygdaloid nucleus; MN-POA/AH, (sexually dimorphic) male nucleus of the preoptic area/anterior hypothalamus (ferret); MPOA/AH, medial preoptic area/anterior hypothalamus; mRNA, messenger ribonucleic acid; MSH, melanocyte stimulating hormone; NO, nitric oxide; NOS, nitric oxide synthase; OHF, hydroxyflutamide; P, progesterone; PGE2, prostaglandin E2; POE, parent of origin effect; POM, sexually dimorphic medial preoptic nucleus (quail); PR, progesterone receptor; sc, subcutaneous; SDN, sexually dimorphic nucleus; SPFp, subparafascicular nucleus ; SRC-1, steroid receptor co-activator 1; Sry, sex determining region of the Y chromosome; T, testosterone; Tfm, testicular feminization; TH, tyrosine hydroxylase; TP, testosterone propionate; VMH, ventromedial hypothalamic nucleus; VNO, vomeronasal organ; WT, wild type

## 1 Introduction

Contemporary textbooks of behavioral endocrinology (Nelson, 2000; Becker et al., 2002) list the first formal experiment in this field as having been carried out at the University of Gottingen, Germany by Arnold A. Berthold (Berthold, 1849), who demonstrated that castrating young male chickens prevented the development of crowing, sexual behavior, and secondary sex characteristics, including a red comb. By contrast, castrated chickens that were implanted with a testis (either one of their own or from another male) showed normal male-typical development of a comb along with courtship and sexual behaviors. The implanted testes were vascularized and they produced sperm along with an endocrine product that stimulated the observed behavioral changes, including mating. Many years later it was found that testosterone (T), secreted by Leydig cells of the testes, was the relevant endocrine signal that caused all of these behavioral and somatic effects. These early observations laid the groundwork for a myriad of experiments, conducted mainly in avian and mammalian species, on the actions of T in both the nervous system and in other androgen-sensitive target tissues including the prostate gland and penis. Androgens can act directly in the brain to facilitate the expression of numerous social behaviors, including mating. Through its action on

another androgen-sensitive tissue, the penis, androgen also indirectly affects the patterning of mating behavior. This chapter concentrates on the actions of T, and its metabolites estradiol (E) and 5α–dihydrotestosterone (DHT), in the adult and/or fetal brain that contribute to male-typical sex partner preference, sexual arousal including penile erection, and the control of courtship and mating behaviors in male mammals. The reversible, adult (so-called activational), the permanent perinatal (so-called organizational), and the pubertal actions of testosterone and its neural metabolites on neural mechanisms controlling male-typical sexual behavior are considered. Experimental findings from several vertebrate species including rat, ferret, mouse, hamster, quail, monkey, and human are used to illustrate the relevant principles of neuroendocrine regulation. Extensive reviews of the literature on the neuroendocrine and neurochemical regulation of male sexual behavior (Hull et al., 2002), as well as of brain and behavioral sexual differentiation (Wallen and Baum, 2002; De Vries and Simerly, 2002), appeared in 2002. I therefore concentrate here on studies concerning the neuroendocrine regulation of masculine sexual behavior that were either not highlighted in those reviews or have been published since 2001.

## 2 Methods of Studying Appetitive versus Consummatory Components of Male Sexual Behavior as well as Erectile Function

A distinction between the neuroendocrine mechanisms controlling appetitive and consummatory components of male-typical sexual behaviors is emphasized throughout this review. Much research using animal models has concentrated on the different neuroendocrine mechanisms controlling sexual motivation, penile erection, and mating behavior per se. The most common model system is the male rat in which mating performance has been observed during interactions with an estrous female. In this situation, a receptive female is placed in a chamber with the male being tested, and the observer records the occurrence of mounts with pelvic thrusting, penile intromissions, and ejaculations over time. In rats, as in many rodent species, the male displays a series of discrete mounts of the female partner that are accompanied by very brief penile erection, pelvic thrusting, and intromission into the vagina. The male dismounts after each intromission. After 5 to 15 such mounts with intromission, the male ejaculates a copulatory plug composed of secretions of the prostate, seminal vesicle, and coagulating gland and sperm from the testes. Deposition of this copulatory plug against the female's cervix ensures that sperm will pass into the uterus, thereby increasing the likelihood that fertilization of ova will occur in the female's fallopian tubes. Receipt of a minimal number of intromissions from the male over a particular period insures the activation of a neuroendocrine reflex in female rodents, which is needed to stimulate prolactin secretion from the pituitary gland. Prolactin then stimulates the corpora lutea of the ovaries to produce the progesterone needed to establish pregnancy (Erskine, 1995).

Significant species variations exist in the behavioral patterns displayed by male vertebrates during mating. For example, many species of fish perform stereotyped courtship movements that entice the female to deposit eggs in a nest, whereupon the male positions himself over these eggs and deposits his sperm without any physical contact with the female. Male birds exhibit a wide variety of courtship displays, including vocalization (crowing or singing), strutting, mounting, and deposition of sperm through direct cloacal contact with the female. The pattern of mating displayed by the male rhesus monkey resembles that shown by the male rat, as described earlier. By contrast, the male ferret mates by grasping the female's neck, mounting, and exhibiting episodes of pelvic thrusting (accompanied by penile erection). Once the erect penis is inserted into the female's vagina, thrusting ceases, and the intromission is maintained for up to 1.5 h, even after ejaculation occurs. This intromissive stimulation activates a neuroendocrine reflex in females leading to the pituitary secretion of luteinizing hormone (LH) and subsequent ovulation (Carroll et al., 1985). Specific patterns of masculine courtship and coital behavior have evolved in different species (Dewsbury, 1972) to maximize the chances of reproductive success.

Recording the frequency or timing the duration of neck grip, mounting, intromission, and ejaculation provides a useful index of masculine coital performance. However, these variables provide only partial insight into an animal's level of sexual motivation. Sexual motivation is a construct that refers to the inclination of an individual to seek out and approach a partner for the purpose of mating. Masculine sexual

motivation has been studied in several different ways. These include (Stone et al., 1935) monitoring the willingness of male rats to cross an electrified grid to gain access to an estrous female, as well as latencies of males to approach an estrous female tethered in the goal box of a straight runway (Beach and Jordan, 1956; Bolles et al., 1968; Lopez et al., 1999). Another approach has been to require rats to press a lever in a Skinner box to gain access to an estrous female (Beck, 1971). A shortcoming of this method is that subjects' operant responses occurred at a low rate under a continuous reinforcement schedule, and when the female became available, the resulting sexual interaction disrupted subjects' operant lever-pressing behavior. Everitt et al. (1987) improved on this procedure by providing male rats with a conditioned secondary reinforcer (a red light) that was initially associated with access to an estrous female that dropped into the male's compartment from an overhead location. This procedure led to high levels of lever pressing by male subjects in order to illuminate the conditioned stimulus. Although some interesting data were obtained using this method, it also had certain disadvantages in that considerable pretraining was needed for subjects to acquire the task, and various experimental manipulations could influence task performance by affecting subjects' motivation to lever press for the conditioned stimulus as opposed to the unconditioned sexual stimuli.

The method of measuring runway-approach latencies is insensitive and the method of training animals to press a lever for access to a goal stimulus is tedious. As a compromise, numerous investigators have chosen to assess the subjects' preference to approach and interact with any one of two different social stimuli that are tethered to the opposite ends of a 3-compartment box or in the goal boxes of a T- or Y-shaped maze. This method has also been used to provide a choice between volatile odors from anesthetized conspecifics and physical access to these animals. Such an approach has been used to assess the preference of rats (Vega Matuszczyk et al., 1988), hamsters (Johnson and Tiefer, 1972), ferrets (Stockman et al., 1985), and mice (Bakker et al., 2002) for same-sex versus opposite-sex conspecifics. This method has also been extensively used (Winslow et al., 1993) to establish the roles of vasopressin and oxytocin in monogamous pair bonding in male and female prairie voles, respectively. The motivation of male ferrets to approach same-sex conspecifics in a T-maze was studied after the placement of lesions in the sexually dimorphic preoptic/anterior hypothalamic region (Paredes and Baum, 1995). More recently, this method was adapted so that volatile odors from same-sex versus opposite-sex conspecifics could be presented in an air-tight Y-maze, with the aim of establishing the role of body odorants in heterosexual mate recognition in ferrets of both sexes (Kelliher and Baum, 2001). Avian species use visual signals to identify preferred mating partners, and the time that male quail spend approaching a window to view a receptive female has been taken as an index of their sexual motivation (Balthazart et al., 1998).

Sexual motivation in male rats and mice has been assessed using bilevel test chambers. Males' level-changing behavior increased significantly when subjects were tested in the presence of an estrous—as opposed to an anestrous—stimulus female (Mendelson and Pfaus, 1989). Anosmic male rats showed less level changing in the presence of an estrous female (Van Furthand Van Ree, 1996b), implying that males' motivation to approach the female resulted from their attraction to volatile estrous odors. Male rats showed significantly less level-changing behavior within a few minutes following ejaculation with an estrous female (i.e., during the postejaculatory interval) (Van Furth and Van Ree, 1996a), providing further evidence that this behavior is a useful index of the males' sexual motivation. Male rats that were treated with dopamine (DA) receptor blockers also showed significantly less level-changing behavior in the presence of an estrous female (Pfaus and Phillips, 1991), implying that the activation of DA neurons normally augments masculine sexual motivation and reward.

A simple method for assessing the rewarding characteristics of drugs of abuse (e.g., heroin, cocaine, amphetamine) has been to demonstrate that the administration of a particular drug in a compartment (distinctive because of its color, odor, and/or floor texture), which was initially not preferred by a subject, causes the subject to prefer that compartment as a result of repeated pairing of its physical features with receipt of the drug (Mucha et al., 1982). Male rats learn a conditioned place preference (CPP) for the opportunity to mate with an estrous female (Miller and Baum, 1987). This type of CPP was less evident in male subjects that had no control over the rate at which an estrous female allowed mounting and intromission behaviors to occur (Martinez and Paredes, 2001).

In addition to the above-mentioned methods for measuring sexual motivation and mating performance, per se, several model systems have been established in which to study the neuroendocrine regulation

of penile erection in mammals. In many commonly studied laboratory species, penile erections can be easily observed and counted "in copula" with the use of a mirror for ventral viewing during mating sessions with a female conspecific. More detailed measurements of erectile function, including monitoring blood pressure increments in the penile corpora cavernosa that are associated with erection induced by electrical stimulation of the cavernosal nerve, have been made in studies using anesthetized male rats (Lugg et al., 1995; Marin et al., 1999) and rabbits (Traish et al., 1999). Numerous experiments have also been conducted in which erectile function was studied "ex copula" in awake male rats during whole body restraint and retraction of the penile foreskin coupled with continuous pressure at the base of the penis (Hart, 1967). Finally, erection has also been studied ex copula by placing an awake male rat down wind from an estrous female whereupon noncontact, psychogenic erections induced by volatile chemosensory signals from the female are observed using a ventrally placed mirror (Sachs, 1997).

## 3 Activation of Male-typical Sexual Behavior and Penile Erection by Testosterone and its Neural Metabolites, Estradiol and Dihydrotestosterone

### 3.1 Effects of Castration and Systemic Administration of Steroids or Antagonist Drugs

With one notable exception (discussed later in detail), studies conducted over the past 75 years have established the indispensable role of the testicular steroid hormone, T, in promoting the activation of both appetitive and consummatory components of sexual behavior among infra primate mammalian species (Hull et al., 2002). Thus, castration of male rodents (e.g., rats, mice, hamsters, and guinea pigs) inevitably leads to a steady decline over a period of several weeks in ejaculation, followed by a decline in mounting and approach of an estrous female. Administration of T immediately after castration will maintain high levels of male-typical mating behavior, and this treatment will readily restore mating in castrated males even when treatment is begun many months after the postcastration disappearance of sexual behavior. Evidence will be considered suggesting that T, either acting itself or after metabolism in the brain into E or DHT, plays a permissive role in the sense that it facilitates the display of appetitive and consummatory sexual behaviors in response to olfactory, visual, and/or genital–somatosensory stimuli derived from a sexually receptive estrous female. In the absence of circulating T, these same stimuli lack the ability to elicit sexual behaviors. Adult male rats normally have circulating levels of T that range from 1 to 3 ng/ml; however, sexual behavior can be readily maintained in castrated rats by s.c. administration of very low doses of T that result in plasma levels of <1.0 ng/ml (Damassa et al., 1977). Higher circulating levels of T are required to restore mating in long-term castrate males. Male mammals normally begin displaying mating behavior around the time of puberty, when testicular production of T and the production of mature sperm is established (55–65 days postnatal in male rats). The first display of sexual behavior can be significantly advanced by daily administration of testosterone priopionate (TP) to prepubertal male rats (Stone, 1940; Baum, 1972), and the doses of TP required for these effects are considerably higher than those needed to maintain or restore mating in adult castrated males. In male hamsters that were castrated either prepubertally or after the age of puberty, s.c. administration of different doses of T (pellets given s.c.) activated all aspects of mating in the adult, but not the prepubertal males (Meek et al., 1997), suggesting that males' ability to respond behaviorally to T increases as they pass through the age of puberty.

Early in the history of contemporary behavioral neuroendocrinology, Beach argued that the activational effect of T on male rats' sexual behavior reflected the increased size and sensitivity of somatosensory receptors on cornified papillae of the glans penis (Beach and Levinson, 1950). Evidence that this peripheral action of T—presumably acting via the androgen receptor (AR) agonist actions of its metabolite, DHT—cannot account for the behavioral effects of T, came from the observation (McDonald et al., 1970; Feder, 1971; Whalen and Luttge, 1971) that administration of DHT to castrated male rats failed to activate mating behavior, whereas it stimulated the growth of the prostate gland and other accessory sex organs, including the penis, up to levels characteristic of testes-intact controls. By the early 1970s, it also became apparent that