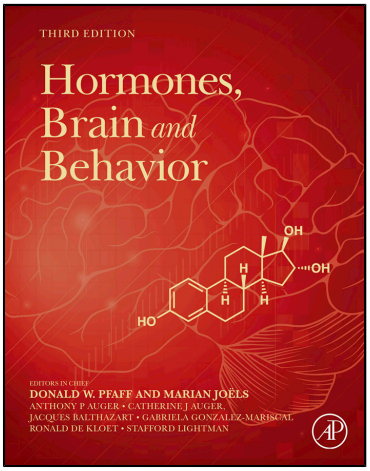

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1.05 Hormones and the Development and Expression of Aggressive Behavior

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Glossary

Aggression A form of social interaction that includes threat, attack, and fighting.

Hormone response element Sequences of DNA in promoter regions that are bound by hormone receptors. Binding of the receptor complex promotes transcription.

Immediate early gene A gene that is expressed rapidly and transiently in response to various cellular stimuli. Several of these genes are used by neuroscientists as indirect markers of neuronal activity because they are expressed when neurons fire action potentials.

Intermittent explosive disorder A disorder characterized by repeated episodes of aggressive, violent behavior that is grossly out of proportion to the situation: thought to affect as many as 7.3% of adults in the United States.

Lifetime History of Aggression (LHA) Scale An interview-based scale that is used by mental health workers to assess general aggressive tendencies in humans. Interviews can be supplemented with other sources such as clinical records.

Organizational/activational hypothesis The proposal that early androgen exposure permanently organizes the nervous system of mammals in a male-like manner. After pre- or perinatal organization by androgens, these hormones more readily activate male-typical postpubertal behaviors by acting upon the organized structures.

Piloerection The erection of hair on the skin, used as a threatening display by many animals.

Hormones, Brain and Behavior, Third Edition, 2017, 145–173

1.05.1 Introduction

Aggression may be defined as overt behavior with the intention of inflicting harm or the threat of harm upon another individual. Aggressive behaviors range from lethal to subtle. The possibility for aggressive behavior exists whenever the interests of two or more individuals conflict (Svare, 1983). Conflicts typically arise over limited resources including territories, mates, and food. Among social species, conflicts may arise over social status and limited resources. A social interaction decides which individual gains status or access to the contested resource. In many cases, a submissive posture or gesture from one individual avoids actual combat. Individuals may also participate in threat displays or ritualized combat in which dominance is determined, but no physical damage is inflicted. Species- and situation-specific rules exist to regulate aggression. When aggressive behaviors break these rules or when the aggression is excessive to situational norms, then it may be considered to be pathological or violent (Haller and Kruk, 2006; Miczek et al., 2007). Pathological or violent aggression causes much personal and societal suffering and thus is an important topic for study. Treatment for violent or pathological aggressive behavior remains primitive. Essentially, no effective interventions exist for violent humans – the most common 'treatment' for violent people is incarceration (Eastman and Campbell, 2006). Remarkably, a death sentence is the sole treatment for an aggressive dog that bites a person. Thus, understanding the pathophysiology of aggression remains an important, yet understudied endeavor.

Indeed, in common with categorizing human behavior, it is often difficult for observers to draw the line between adaptive aggression and pathological aggression in nonhuman animals (Sluyter et al., 2003). An important strategy for improving our ability to draw this line is to understand the mechanistic basis for both species-specific aggression and pathological aggression. This review will examine the role of neural circuits, development, and neuroendocrine mechanisms in the regulation of aggression, primarily in species-specific aggression. Under certain conditions, aggression can deviate from normal patterns (Miczek et al., 2013). Although these models are beginning to provide important insights into potential mechanisms of violence, it is necessary to first understand the basis for normative forms of aggression.

Mechanistic studies of aggression have historically focused on aggression in nonpathological states, and in this state gonadal hormones play an important role. Across most species, males are more aggressive than females, and this difference usually emerges at puberty, which coincides with important sex differences in gonadal hormone secretion. These patterns have contributed to a historic focus on the role of gonadal hormones such as testosterone in the regulation of aggressive behaviors. Initial studies using hormone ablation and replacement approaches showed a clear role for androgens such as testosterone in many species (Vandenbergh, 1971; Leshner and Moyer, 1975; Soma, 2006). However, exceptional cases appeared in which removal of testes had no obvious effect on aggression (Demas et al., 1999; Trainor and Marler, 2001). Furthermore, for many years the link between testosterone and aggression in humans appeared very weak (Archer, 1991). These apparently inconsistent observations raised the question of whether neuroendocrine mechanisms of aggression were evolutionarily conserved. However, improved experimental design and methodologies have provided new insights. For example, androgens can be synthesized *de novo* within the brain (Pradhan et al., 2010), so removal of testes does not necessarily remove all sources of testosterone. In addition, rapid changes in testosterone (rather than baseline levels) are now known to have important effects on aggression (Gleason et al., 2009). Improved experimental designs have revealed that pairing testosterone measurements with competitive tasks are more effective at revealing hormone-behavior relationships in humans (Section 1.05.4.2). Hormones affect aggression by acting on neural circuits in the brain, and these circuits have been identified using lesions, immediate early gene studies, neuropharmacology studies, and more recently optical stimulation. Within these neural circuits neurotransmitters such as serotonin have important modulatory effects on aggression. Finally, experience has important effects on how these neural circuits respond in competitive contexts. These effects of experience occur across development, both early in life and in the adult.

1.05.1.1 Categories of Aggression

Several categories of aggression are generally recognized, and the different types of aggression have different neuroendocrine bases. For example, there are important differences in the neuroendocrine mechanisms of maternal aggression versus territorial aggression, but there is also a significant degree of overlap. Androgens (Bouissou, 1983) and estrogens (Laredo et al., 2014b) have important modulatory effects on intermale aggression, especially in territorial contexts. Hormonal changes associated with the pregnancy, including high levels of estrogens, have an important role for inducing maternal aggression (Gammie et al., 2007). In the most widely studied rodent species (domestic mice and rats), maternal aggression is the main form of aggression in females. However, in other rodent species such as Syrian hamsters intrafemale aggression is more prevalent (Gutzler et al., 2010; Staffend and Meisel, 2012), which provides opportunities for examining neuroendocrine mechanism of female aggression outside of the context of reproduction. Another type of agonistic behavior commonly studied in the laboratory has been called fear-induced aggression, but this is more correctly termed 'defense' and is not strongly modulated by estrogens or androgens (Blanchard and Blanchard, 1989). Recently there has been increased interest in abnormal forms of aggression (or escalated aggression) that might resemble aspects of human violence. Abnormal aggression has been characterized using quantitative or qualitative criteria (Natarajan and Caramaschi, 2010; Miczek et al., 2013). Aggression can differ quantitatively such as induction with low provocation or occur at higher intensity. Alternatively, aggression can differ qualitatively such as through attacks directed at vulnerable regions or through a lack of responding to submissive displays that normally trigger cessation of aggressive behavior. Abnormal aggression can be induced by very low glucocorticoid levels induced by adrenalectomy (Haller et al., 2001). Intriguingly, in this context aggression occurs in the absence of autonomic activation, which is observed in some forms of human violence.

Whereas specific aggressive behaviors in animals are typically highly stereotyped (wrestling, chasing, bites), aggression behaviors in humans can take many forms (e.g., physical versus verbal). Quantifying aggression in humans is a challenge. Early efforts to study aggression relied primarily on self-reports of aggression that estimated general aggressive tendencies. These measures generally correlate poorly with neuroendocrine measures such as testosterone (Archer, 2006). However, a variety of tasks have been developed to induce aggressive behavior under controlled conditions (e.g., point subtraction task). Aggressive behavior in these tasks is more closely linked to testosterone levels, which are rapidly modulated during aggressive interactions (Carré et al., 2011). These tests also induce sympathetic nervous system activation (Gerra et al., 2007). Increased arousal and anger are main components of what has been termed reactive aggression (Vitiello and Stoff, 1997), which is considered to be more impulsive yet can lead to sustained aggressive responses. It has been thought that reactive aggression accounts for most societal problems related to aggression (Blair et al., 2006). Reactive aggression is usually associated with impulse control and low serotonergic signaling (Mehlman et al., 1994; Krakowski, 2003). In contrast instrumental aggression occurs in the absence of physiological arousal and is considered to be a more goal-oriented behavior. High-profile incidents (e.g., mass killings, genocides, or assassinations) are likely to reflect instrumental mechanisms of aggression. Attacking or otherwise bullying your neighbors to intimidate them is another example of instrumental aggression. The controlled–instrumental subtype of aggression is thought to be regulated by higher cortical systems and less dependent on the hypothalamic and limbic systems that are known to mediate impulsive aggression (Viding et al., 2007; and see below), and likely less dependent on hormones than other types of aggression.

Mental disorders such as intermittent explosive disorder and posttraumatic stress disorder are associated with increased autonomic arousal, which can contribute to sudden and uncontrolled reactive aggression (Blair et al., 2006; Viding et al., 2007). In contrast, individuals who are diagnosed with conduct disorder or antisocial personality disorder show unusually low autonomic responsiveness (Viding et al., 2007), which can contribute to increased instrumental aggression by blunting the typical emotional responses (Raine, 2002). Thus, exaggerated aggressive responses can be observed in both high- and low-arousal states, with different biochemical, neuroanatomical, and neuroendocrine systems contributing to behavior in each context. These results illustrate that more than one approach to studying neuroendocrine mechanisms of aggression will be required. Animal model studies in which testosterone has an important modulatory effect on aggression will be more informative for reactive aggression whereas approaches examining aggression under low-arousal conditions may be more informative for understanding instrumental aggression.

Aggressive behavior is a motivated behavior. In common with other motivated behaviors, four types of questions arise: (1) What are the external factors that elicit aggressive behavior? (2) What neural circuitry mediates aggressive behaviors? (3) How does aggression develop across ontogeny? (4) What are the internal signals that mediate aggressive behaviors? Here we will focus on questions 2–4. First we will review animal models and tests of aggression, because much of what is known about neurobiological mechanisms and development of aggression is based on animal models.

1.05.2 Animal Models and Tests of Aggression

The rigorous quantification of aggressive behaviors is an essential requirement for identifying underlying neuroendocrine mechanisms. The most common behavior test for quantifying overt aggressive behaviors is the resident–intruder test (Koolhaas et al., 2013). In a typical test the focal animal is housed in a home cage for at least 3 days. This allows the focal animal to become familiar with home cage and adopt it as a territory. Next an unfamiliar intruder is introduced into the cage. The introduction of the intruder usually prompts the initiation of anogenital sniffing by the resident, which results in the detection of nonvolatile pheromones. Depending on the species or strain, aggressive threats such as tail rattles or vocalizations may precede overt aggressive behaviors (Nelson and Chiavegatto, 2000). In rats and mice, attacks are usually directed toward the flanks which have thick skin that prevent wounding. Each occurrence of these behavioral elements can be measured in terms of frequency, as well as the onset and termination of specific behaviors from both live observations and video records. An advantage of the resident–intruder test is that it can be used in several different contexts, which can allow the study of several forms of aggression.

In many cases androgens either promote aggressive behavior in the resident–intruder test (Vandenbergh, 1971; Lima and Spinelli de Oliveira, 2014) or are secreted in response to engaging in aggression (Marler et al., 2005). These contexts appear to correspond to reactive aggression in humans, which is more likely to be linked with increases in testosterone (Carré et al., 2011). Under these conditions residents typically reduce aggression in response to the intruder engaging in submissive postures. However, when adrenalectomized rats are tested as residents in this test, submissive displays by the intruder are ignored resulting in escalated aggression (Haller et al., 2001). It is thought that aggression under these conditions more closely resembles the instrumental aggression associated with conditions such as conduct disorder (Haller and Kruk, 2006).

Aggression can also be observed in females using the resident–intruder test. Most often this is studied in lactating dams with male intruders. Maternal aggression under these contexts is considered defensive aggression (Lonstein and Gammie, 2002). It is characterized by short latency attacks of high intensity, mostly directed toward the head/neck region of the opponent and usually without the introductory threatening behaviors typically displayed by male animals confronted with an intruder. In laboratory rats and mice, females are rarely aggressive toward other females. However, female–female aggression is quite prevalent in other species. The Syrian hamster is a solitary species, and females are very aggressive toward other females (Solomon et al., 2007; Staffend and Meisel, 2012). In the California mouse, males and females form monogamous pairs, and females are also very aggressive toward other females (Davis and Marler, 2004; Silva et al., 2010; Trainor et al., 2010b). These species allow for the ability

to examine whether neuroendocrine mechanisms of aggression identified in males extend to females (Gutzler et al., 2010).

The resident–intruder test can be adapted to examine exaggerated aggressive behavior following provocation. In this protocol an intruder is first placed into the resident's home cage behind a protective barrier, which is then removed (Miczek et al., 2013). Elevated aggression using this protocol can be observed in both males (Fish et al., 1999) and females (Potegal, 1991). This approach may provide insights into mechanisms contributing to exaggerated aggression following perceived provocation.

Under normal conditions, it is rare for male domestic mice and rats to direct aggression toward females. However among humans, women are often targets of male violence (Crowell and Burgess, 1996). Recently it was discovered that male rats exposed to psychosocial stress during the peripubertal period were more aggressive with female breeding partners compared to controls (**Figure 1**; Cordero et al., 2012). Intriguingly this effect was also observed in the male offspring of these pairs. Female-directed aggression by males was reversed with monoamine oxidase inhibitor (Marquez et al., 2013). A recent prospective study reported that individuals that were neglected as children were more likely to injure an adult intimate partner (Widom et al., 2014). However, the neurobiological mechanisms contributing to this effect are unknown. Rodent peripubertal stress models may facilitate the identification of physiological mechanisms contributing to intersex aggression. Clearly, disrupting generational transmission of this form of aggression is an important public health problem.

The resident–intruder test can provide insights into mechanisms of aggression in multiple contexts. However, several factors need to be considered when interpreting the outcome of this test. For example, the behavior of the stimulus animal, or intruder, has an important impact on the behavior of the focal animal or resident. Previous experiences of the intruder can confound the results. Thus, a previously defeated or naïve intruder can elicit different reactions from the resident. One way that this potential problem can be reduced, however, is to determine which group-housed intruders are not aggressive before the onset of the behavioral tests. An additional source of variability can come from dominance relationships among cage mates. For example, in the widely used C57Bl6 strain, each cage of males has a dominance hierarchy. There are important differences in behavior and brain function between the most dominant and most subordinate cage mate (Howerton et al., 2008). For example, the lowest ranking cage mates had less corticotropin-releasing hormone 2 mRNA and estrogen receptor alpha in the bed nucleus of the stria terminalis than the most dominant cage mate (Greenberg et al., 2014). An easy solution for quantifying this variation is to run mice through a 'tube test,' which provides an accurate estimate of dominance status.

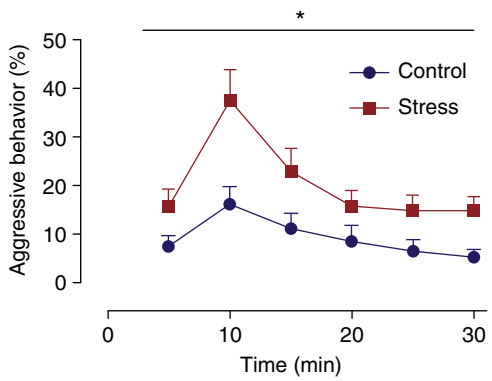

Figure 1 Peripubertal stress–induced abnormal aggressive behaviors in resident–intruder tests performed in adulthood. Aggressive behaviors of resident rats when intruders were similar to the resident rat in body weight (stress effect: $F1, 29 = 9.52$, $p = 0.004$; $n = 15–16$ per group). Reprinted from Marquez, C., Poirier, G.L., Cordero, M.I., Larsen, M.H., Groner, A., Marquis, J., Magistretti, J., Trono, D., Sander, C., 2013. Peripuberty stress leads to abnormal aggression, altered amygdala and orbitofrontal reactivity, and increased prefrontal MAOA gene expression. Transl. Psychiatry 3, e216 with permission from Nature.

Experience is also important in the relationship between hormones and aggressive behavior (Miczek and Fish, 2006). Castration and hormone-replacement studies of males representing several species of reptiles, fish, and birds clearly demonstrate reduced postcastration levels of aggression and restoration of aggression after testosterone treatment (e.g., Crews and Moore, 1986; Wingfield et al., 1987). In mammals, the effects of androgens in supporting aggressive behavior depend largely on experience. Castrated mice and rats without prior aggressive experience rarely fight when tested with another male conspecific (Christie and Barfield, 1979). Individuals that have won aggressive encounters before castration will exhibit aggression long after the testes have been removed (e.g., Christie and Barfield, 1979; DeBold and Miczek, 1981, 1984). Winning aggressive encounters usually induces a temporary surge in testosterone referred to as the challenge effect. The combination of winning experience and testosterone has a powerful enhancing effect on aggressive behavior (Trainor et al., 2004; Fuxjager et al., 2011). Winning also increases the expression of androgen receptors in motivational circuits including the nucleus accumbens and ventral tegmental area (Fuxjager et al., 2010). Interestingly, these motivational circuits are also altered by aggressive experience in female rodents. Female Syrian hamsters also become very aggressive with repeated aggressive encounters (Staffend and Meisel, 2012), and this behavioral change is mediated in part by glutamatergic synaptic plasticity in the nucleus accumbens (Been et al., 2016).

1.05.3 Endocrine Signals' and Receptors' Contribution to Aggression

1.05.3.1 Steroid Hormones

The role of steroid hormones has long been a focus of investigators studying the neuroendocrine bases of aggressive behavior. Although testosterone is generally a key hormone regulating aggression, either directly or by serving as a prohormone for DHT or estradiol, detailed experiments have demonstrated that the relationships between steroid hormones such as testosterone and aggression are complex. Other factors such as steroid hormone synthesis in the brain, differential expression of steroid receptors, and environmental context have important influences on the behavioral effects of circulating hormones.

1.05.3.1.1 Androgens

The idea that hormones produced in the testes promote aggressive behavior dates back to the mid-nineteenth century in the classic experiments of Arnold Berthold (Quiring, 1944). In these studies aggressive behavior in male chickens was abolished by removal of testes and restored when donor testes were implanted. Subsequent castration and hormone-replacement experiments have identified androgens as a key class of hormones produced by the testes that facilitates aggression. Early studies focused on establishing correlations between plasma concentrations of androgens and aggression. Androgen levels are often increased during the breeding season when males aggressively compete for breeding opportunities (Lincoln et al., 1972; Wingfield, 1984; Moore, 1986; Bales et al., 2006). Similarly, male aggressive behavior often increases at the time of puberty (Wallen et al., 1991; Pellis et al., 1997; Delville et al., 2005), when testes mature and begin to secrete androgens. More definitive evidence that androgens facilitate aggressive behavior comes from studies in which androgens are manipulated. Castration reduces male aggressive behavior in Syrian hamsters (*Mesocricetus auratus*) (Vandenbergh, 1971), mice (*Mus musculus*) (Leshner and Moyer, 1975), pigs (*Sus scrofa*) (Zamaratskaia et al., 2008), bulls (*Bos taurus*) (Huxsoll et al., 1998), rats (*Rattus rattus*) (Albert et al., 1987), and red deer (*Cervus elaphus*) (Lincoln et al., 1972), whereas testosterone replacement restores aggression in these species. Similarly, elevated testosterone concentrations via implants increase aggression in a variety of passerine birds (Wingfield et al., 1987; Ketterson and & Nolan, 1992) and spiny lizards (Marler and Moore, 1989).

Strain differences certainly exist among house mice in the extent to which aggressive behaviors are expressed and in the extent to which these aggressive behaviors are mediated by androgens. The effects of castration on predatory, shock-induced, maternal, and isolation-induced aggression were studied in Swiss albino mice. Isolation-induced aggression was generally reduced after castration; postgonadectomy treatment with testosterone, 5α-dihydrotestosterone (DHT), or estradiol restored this form of aggression (reviewed in Brain, 1983). Castration increased intruder aggression toward lactating females, and treatment with testosterone, DHT, or estradiol reversed the elevated rate of aggressive responses in this situation (Brain, 1983). These results imply that steroid hormones do not merely 'trigger' aggression, but act to affect the animal's perception of and response to aggression-provoking stimuli (Haug et al., 1986).

In another series of experiments (Whalen and Johnson, 1987), male mice were pitted against either lactating females or olfactory bulbectomized males (reviewed in Johnson and Whalen, 1988). Gonad-intact males and castrated males treated with testosterone attacked the olfactory bulbectomized males, but did not attack lactating females. Untreated castrated males tended to display tremendous individual differences in aggressiveness, with some attacking either type of opponent, others attacking only one type of opponent, and others displaying no attack behaviors (Johnson and Whalen, 1988). Because castration was associated with large individual variation in aggressive responding, and because androgen treatment reduced that variation, Johnson and Whalen (1988) proposed that testicular steroid hormones act to induce 'behavioral homogenization' to reduce behavioral variability. This is an intriguing hypothesis to account for the disparate aggressive responses of males to different aggression-provoking stimuli, although further experiments are necessary to evaluate it fully.

Although baseline testosterone concentrations regulate aggression in many species, studies have identified several species in which castration does not reduce male aggression (Caldwell et al., 1984; Demas et al., 1999; Trainor and Marler, 2001; Trainor et al., 2006a). Furthermore, dominance in more complex social organizations may not be related to blood concentrations of testosterone, especially in stable groups. For example, dominant dogs or squirrel monkeys can be castrated without affecting their position in the hierarchy (Dixson, 1980). Also, treatment of low-ranking individuals with androgens does not change their status. The intuitive conclusion from these results is that testosterone does not affect aggression in these species. However, there are several ways in which aggressive behavior could be influenced by androgens independent of baseline testosterone concentrations.

Acute hormonal responses to the environment can have different effects on behavior than the baseline hormonal state (Leshner, 1979). Winning aggressive encounters increases male testosterone concentrations ('challenge effect') in birds (Wingfield et al., 1990), fish (Oliveira et al., 2002), rodents (Oyegible and Marler, 2005), nonhuman primates (Rose et al., 1971), and humans (Mazur and Booth, 1998). Interestingly, the increase in testosterone after a winning experience is not observed unless the individual is in a familiar environment (**Figure 2**; Fuxjager et al., 2009). Initially, these rapid and transient responses were puzzling because it was thought that the effects of steroid hormones such as testosterone required at least several hours for a behavioral effect to be observed. It is now apparent, however, that these challenge effects can influence behavior. Transient increases in testosterone may help crystallize the experience of winning an aggressive encounter (Trainor et al., 2004). Several studies have demonstrated that individuals that win aggressive encounters are more likely to win future encounters (Parmigiani and Brain, 1983; Chase et al., 1994; Kudryavtseva, 2000), even when variables such as intrinsic fighting ability are controlled

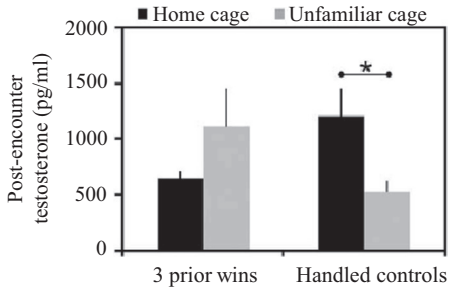

Figure 2 Postencounter levels of testosterone in focal individuals. The bars represent mean hormone levels and the error bars represent the standard error. The * indicates significant differences between treatment groups ($p < 0.025$). The data were log transformed for statistical analysis. Reprinted from Fuxjager, M.J., Mast, G., Becker, E.A., Marler, C.A., 2009. The 'home advantage' is necessary for a full winner effect and changes in post-encounter testosterone. Horm. Behav. 56, 214–219 with permission from Elsevier.

(Oyegible and Marler, 2005). In addition, steroid hormones are now known to exert nongenomic effects which can occur within seconds or minutes (Vasudevan and Pfaff, 2006). Injections of testosterone can act within minutes to reduce anxiety-like behavior in mice (Aikey et al., 2002), and an acute injection of estradiol (a testosterone metabolite) can increase aggressive behavior in *Peromyscus* within 15 min (Nelson and Trainor, 2007; Trainor et al., 2007a). Testosterone can be converted to estradiol within the brain, a conversion mediated by the aromatase enzyme. Environmental factors can rapidly convert testosterone to estrogens in the brain and affect aggressive behaviors in a number of contexts (reviewed in Laredo et al., 2014b).

Steroid synthesis in the brain is not limited to the conversion of androgens to estrogens by the aromatase enzyme. Many of the enzymes required for *de novo* steroid synthesis have been identified in the brain (Baulieu and Robel, 1990; Young et al., 1996; Soma, 2006), raising the possibility that the brain may be producing androgens independently of the testes. Dehydroepiandrosterone (DHEA) is produced in the adrenal gland but requires only two metabolic steps to convert to testosterone (Demas et al., 2007). Studies in hamsters (Demas et al., 2004; **Figure 3**) and song sparrows (Soma et al., 2002) suggest that adrenal steroids may promote aggressive behavior, especially under environmental conditions in which gonadal testosterone secretion is low. Most studied rodents have elevated aggression levels under short-day photoperiods (Jasnow et al., 2000; Trainor et al., 2007b, 2008), an effect that is mediated by extended periods of elevated melatonin concentrations (Jasnow et al., 2002; Laredo et al., 2014a). In hamsters, removal of the adrenal glands blocks the aggression enhancing effects of melatonin (**Figure 3**). This suggests that adrenal steroids are critical for sustaining aggression outside of the breeding season when testosterone concentrations are low. However, in female hamsters, melatonin appears to work directly on adrenal function to elevate DHEA. Short-day female hamsters are more aggressive than their long-day counterparts; long-day hamsters provided with short-day melatonin doses also displayed increased aggression and elevated DHEA concentrations (Rendon et al., 2015). Furthermore, melatonin increased DHEA secretion from cultured adrenal glands. As noted above, testosterone sometimes exerts behavioral effects indirectly through its conversion to estrogens.

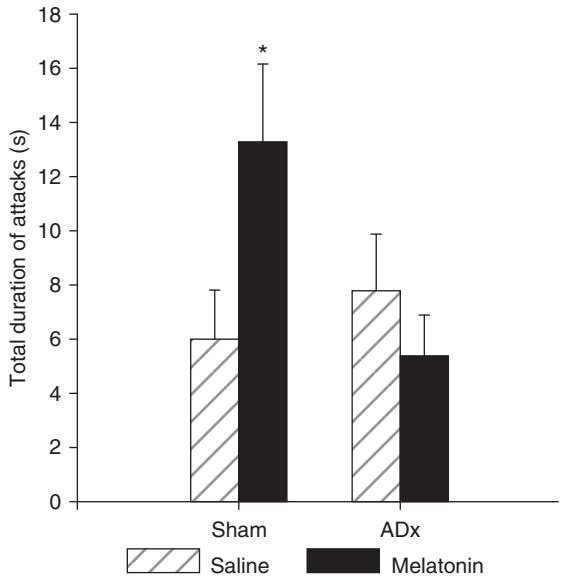

Figure 3 Mean (±SEM) total duration of attacks (s) in hamsters that received bilateral adrenalectomies (ADx) or sham operations (Sham) and subsequently treated with either melatonin or control (Saline) injections. Significant differences between pairwise means are indicated by an asterisk (*) if $p < 0.05$. Reprinted from Demas, G.E., Polacek, K.M., Durazzo, A., Jasnow, A.M., 2004. Adrenal hormones mediate melatonin-induced increases in aggression in male Siberian hamsters (*Phodopus sungorus*). Horm. Behav. 46:582–591 with permission from Elsevier.

Several studies of human aggression in which psychological rating scales were used to quantify levels of aggressiveness or hostility reported no relationship between blood or saliva androgen concentrations and aggressiveness (Doering et al., 1975; Monti et al., 1977; Persky et al., 1977). However, relationships between blood testosterone concentrations and behavior have been reported among aggressive, violent, and antisocial individuals, especially those incarcerated in prison (Kreuz and Rose, 1972; Ehrenkranz et al., 1974). Prison inmates with high circulating testosterone concentrations, usually defined as the top 5% or 10% of the normal distribution, had committed violent crimes (Ehrenkranz et al., 1974; Dabbs et al., 1987, 1988), were more unruly in prison, and were judged more harshly by their parole boards (Dabbs et al., 1987, 1988). High testosterone concentrations have also been associated with male juvenile delinquency (Olweus, 1983). Although some studies of criminal populations show no association between plasma testosterone and violent behavior (for example, Matthews, 1979), the consensus is that violence among prison inmates and blood androgen concentrations are positively correlated. A similar relationship was observed among female prison inmates (Dabbs and Hargrove, 1997).

Two related hypotheses have been proposed to explain the association between high androgen concentrations and human antisocial behavior as observed in delinquent or criminal populations: (1) androgens directly mediate the antisocial activities and (2) androgens promote a constellation of traits, including social dominance, competitiveness, and thrill-seeking, that may be expressed either as antisocial or as prosocial behavior depending upon the individual's resources and background. To distinguish between these two possibilities, a large sample of 4462 US military veterans was examined beginning in 1985. Analyses of their psychological profiles and saliva concentrations of testosterone suggested that androgens directly mediate antisocial behavior in human males, although socioeconomic status has a small moderating effect (Dabbs and Morris, 1990).

Few studies have addressed the role of androgens in aggressive behavior in women; no consistent correlation between androgen concentrations and aggressive behavior has been reported for women (Persky et al., 1977; Dabbs et al., 1988; Dabbs and Hargrove, 1997). However, subtle effects of androgens may influence aggression in women. Saliva testosterone concentrations did not differ between female prison inmates

and female college students. But further analyses discovered that testosterone concentrations were highest in women prisoners convicted of unprovoked violent crimes and lowest in women convicted of 'defensive' violent crimes, such as killing abusive husbands (Dabbs et al., 1988).

1.05.3.1.2 Estrogens

Often considered to be primarily a female class of hormones, estrogens have important effects on many male behaviors including aggression. In most species that have been examined, estrogens increase aggressive behavior. Blocking estrogen production with an aromatase inhibitor reduces aggression in Japanese quail (Schlinger and Callard, 1990) and song sparrows (Soma et al., 2000), whereas aromatase knockout mice display low aggression levels in resident–intruder tests (Toda et al., 2001; Matsumoto et al., 2003). In CFW and CF-1 strains of mice, the negative effect of castration on aggression can be reversed by treatment with estradiol (Simon and Whalen, 1986). The effects of estrogens on aggression can be rapid in both mammals and birds (reviewed in Heimovics et al., 2015).

Estrogens can bind to one of at least two estrogen receptor (ER) subtypes, α and β. Most of what is known about the effects of these receptors on aggression comes from a series of studies on knockout mice. Male mice with targeted disruption of ERα display reduced aggression when tested with other males in a number of testing situations (Ogawa et al., 1997; Scordalakes and Rissman, 2003, 2004). Curiously, male ERα knockout mice are more likely than wild-type mice to attack female intruders. In male CD-1 mice, levels of aggression directed toward other males are positively correlated with the number of ERα immunopositive cells in the LAS, BNST, and AHA (Trainor et al., 2006a). The deletion of ERβ is generally associated with increased aggression (Ogawa et al., 1999; Nomura et al., 2006), although this effect appears to be context dependent (Nomura et al., 2002). Deletion of both receptors is associated with increased male aggression (Ogawa et al., 2000). In these knockout studies, the effects of ERα and ERβ could be organizational, activational, or both. Studies using ER-specific ligands in adult animals have suggested that the directional effects of these ERα and ERβ may occur primarily during development (see Section 1.05.7.1), although additional studies are needed to test this hypothesis.

1.05.3.1.3 Glucocorticoids

The effects of glucocorticoids on aggression are also variable, although the mechanistic basis for this is poorly understood. Generally, chronic elevations in glucocorticoid concentrations (usually associated with stress) inhibit aggressive behavior (Leshner et al., 1980; Maestripieri et al., 1991; Summers et al., 2005), whereas chronic deficiencies in glucocorticoid secretion are associated with increased aggression (Haller et al., 2001, 2004). Elevated baseline glucocorticoid concentrations inhibit testosterone secretion (Viau, 2002), increase sensitivity to serotonin (Meijer and de Kloet, 1998), and increase glutamate neurotransmission in frontal cortex (Moghaddam, 2002). All of these physiological responses could contribute to reduced aggressive behavior and appear to do so in animals subjected to chronic social defeat (Haller, 2014). However, the immediate effect of a transient increase in glucocorticoids on aggression is quite different than a chronic increase in baseline concentrations. Corticosterone acts rapidly to increase aggression in rats (Mikics et al., 2004), hamsters (Hayden-Hixson and Ferris, 1991), and mice (Poole and Brain, 1974). The increase in aggression due to acute elevated corticosterone is particularly salient in challenge-situations, for example, when confronted with unfamiliar opponents or other novel situations (Mikics et al., 2007). In rough-skinned newts (*Taricha granulosa*) corticosterone acts rapidly to promote mating behavior (Moore and Miller, 1984), an effect that has been linked to nongenomic hormone action (Orchinik et al., 1991). This raises the possibility that the effects of chronic elevation of glucocorticoids on aggressive behavior are mediated by changes in gene expression (via activation of mineralocorticoid and glucocorticoid receptors), whereas the effects of a transient increases in glucocorticoids are mediated by nongenomic responses of membrane receptors.

1.05.3.2 Anabolic Steroid Abuse and Aggression

The use of anabolic steroid hormones (such as testosterone) as performance-enhancing drugs has become a high-profile topic in the news media, especially as several elite athletes have been disqualified or stripped of titles or medals. Anabolic steroids are used because they stimulate the growth and development of muscle tissue. Although anabolic steroids have certain therapeutic uses (Ferrando and Wolfe, 2007), when used in excess or abused they have many negative side effects such as infertility, suppressed immune function, and increased risk of cardiovascular, liver, and kidney disease (Bahrke and Yesalis, 2004; Bonetti et al., 2008). In addition there is accumulating evidence that anabolic steroid abuse has adverse psychological effects, including aggression. Surveys have indicated that anabolic steroid abusers are more likely to engage in verbal aggression, fighting, violence toward women, and risk-taking behaviors (Choi and Pope, 1994; Pope and Katz, 1994; Galligani et al., 1996). However, there are some inconsistencies across studies, and study participants may not be forthcoming about their usage, especially because anabolic steroids are outlawed in many countries (McGinnis, 2004). To address whether many commonly abused anabolic steroids exert effects on aggression, researchers have developed animal model systems in which dosages and environmental variables are controlled.

Studies in hamsters and rats have established that many commonly abused anabolic steroids can influence aggressive behaviors, although in some cases these effects depend on testing conditions. Methyltestosterone, but not stanozolol (a nonaromatizable androgen), increases male aggressive behavior in castrated male rats compared to castrated rats receiving oil injections (Clark and Barber, 1994). Other studies in rats (Farrell and McGinnis, 2004) and mice (Martinez-Sanchis et al., 1996) have also reported that stanozolol does not increase aggression (**Figure 4**). Nandrolone is another commonly abused androgen, but its effect on aggressive behavior in rodents is variable. One study reported that nandrolone administration to male rats increased aggression (Long et al., 1996), whereas two other studies observed that nandrolone administration had no effect on aggressive behavior in rats (McGinnis et al., 2002a,b). It has been hypothesized that the effects of nandrolone on aggression may depend

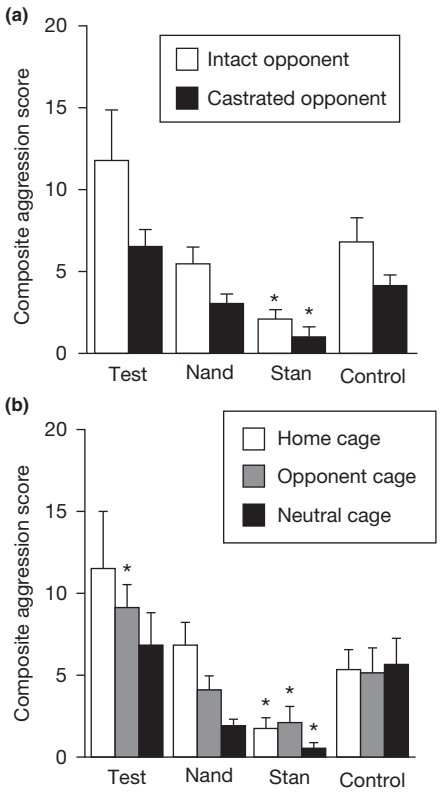

Figure 4 Social discrimination is seen in aggression toward a gonadally intact versus a castrated male opponent (a). Environmental discrimination is depicted in (b). Aggression is shown toward a gonadally intact male in the anabolic androgenic steroid (AAS) males' home cage, the opponents' home cage, or a neutral cage. The rats were treated with testosterone (Test), nandrolone (Nand), Stanozolol (Stan), or vehicle (Control). $^{*}p < 0.05$. Reprinted from Farrell, S.F., McGinnis, M.Y., 2003. Effects of pubertal anabolic-androgenic steroid (AAS) administration on reproductive and aggressive behaviors in male rats. Behav. Neurosci. 117, 904–911, with permission from American Psychological Association.

on experience or testing conditions (McGinnis, 2004). For example, tail pinching can be used as a form of physical provocation (Miczek et al., 2004), and this can exaggerate the effects of anabolic steroids on aggression (McGinnis et al., 2002a). A further complicating factor is that many abusers of anabolic androgens use more than one steroid simultaneously, a practice also known as stacking (Trenton and Currier, 2005). Studies in hamsters show that activation of 5-HT_{1B} receptors blocks the effects of an androgenic cocktail (testosterone cypionate, nortestosterone, and dihydroxytestosterone) on aggression in a resident–intruder test (Grimes and Melloni, 2005). Although stanozolol treatment alone reduced aggressive behavior in male rats, stanozolol treatment with testosterone increased aggression in aggression tests preceded by a tail pinch (Wesson and McGinnis, 2006). Anabolic androgens appear to affect aggressive behaviors by working at several biochemical and neurobiological levels. In hamsters, anabolic androgen administration increases arginine vasopressin (AVP) immunoreactivity (Grimes et al., 2007) and baseline c-fos immunoreactivity (Ricci et al., 2007) in the anterior hypothalamus, a forebrain region that facilitates male aggressive behavior. There is also evidence that anabolic androgens can downregulate GABAergic neurotransmission, thereby facilitating aggressive behavior (Henderson et al., 2006). The emerging picture then is that anabolic androgens facilitate aggressive behaviors by affecting several biochemical pathways and these neurochemical changes are influenced by environmental factors.

Androgenic anabolic use is also a problem of adolescence. According to the 2005 Monitoring the Future Survey, over 3% of 12th-grade males in the United States report having used anabolic androgens (http://www.nida.nih.gov/ResearchReports/Steroids/AnabolicSteroids.html). Anecdotally, anabolic steroid use by adolescents is associated with irritability and heightened aggression, but a causal link has not been established. On the other hand, animal studies have provided compelling evidence for anabolic steroid-induced aggression in adolescent males. Adolescent male hamsters treated chronically with an anabolic steroid cocktail have shorter attack latencies and a greater number of attacks and bites toward a male intruder compared with untreated males (Melloni et al., 1997; Harrison et al., 2000), and anabolic steroid-induced increases in aggression are more robust in adolescent than in adults (Salas-Ramirez et al., 2008). These effects are all the more striking considering that male–male aggression in hamsters is not under strong activational influences by endogenous testosterone. Similarly, a mild provocation (tail pinch) produces a persistent increase in aggression in adolescent male rats treated with anabolic androgens, including aggression toward females (Cunningham and McGinnis, 2007). Importantly, adolescent exposure to anabolic androgens causes long-lasting changes in agonistic behavior (Grimes and Melloni, 2006), neurotransmitter systems (Grimes and Melloni, 2006; Ricci et al., 2007), and synaptic organization (Cunningham and McGinnis, 2007) that persist even after the period of drug exposure. In light of the evidence that endogenous testosterone organizes aggressive behavior during puberty and adolescence, it seems likely that anabolic steroid use during adolescence would result in larger magnitude or more enduring effects on the brain and aggressive behavior than use in adulthood. Taken together, the evidence suggests significant aggression-promoting effects on aggressive behaviors (e.g., Oberlander and Henderson, 2012).

1.05.4 Brain Regions Contributing to Aggression

A complicating factor in studying neural circuits affecting aggression is that many brain nuclei that regulate aggression also affect other social behaviors. For example, in rodents the medial amygdala (MEA) is activated during both aggression and reproductive behavior (Kollack-Walker and Newman, 1995; Choi et al., 2005). Although there are sometimes subtle anatomical differences in activity as measured with immediate early genes (Holt and Newman, 2004), more detailed analyses will be necessary to sort out whether different cell types are activated in different contexts, or whether different cellular responses result in different behavioral responses. Despite this uncertainty, it is clear that a common set of hypothalamic and limbic brain areas play a role in regulating some form of aggressive behavior in a variety of species. Homologous brain

structures appear to regulate social behaviors, including aggression, in both mammalian and nonmammalian species (Gregg and Siegel, 2001; Crews, 2003; Goodson, 2005). Aggression is a primitive, yet highly conserved vertebrate behavior, and it is reasonable to expect that the molecular mechanisms underlying aggression are also similar (and possibly ancient) among vertebrates. Species-specific features of aggression are likely the result of adaptive 'co-opting' of novel molecules as modulators that are 'added to' the primary neural circuits. These findings support the hypothesis that at least some neurobiological and neurochemical mechanisms governing the motivation to engage in aggressive behavior are evolutionarily conserved (Scott, 1975). Thus, results from studies of aggression in rodents and other nonprimate species should provide insight on the motivational circuits regulating aggression in other species, including humans.

1.05.4.1 Studies in Rodents

In rodents, sensory input from the olfactory bulbs (DaVanzo et al., 1983) is sent to the MEA and then relayed to the bed nucleus of the stria terminalis (BNST), medial preoptic area (MPOA), lateral septum (LAS), anterior hypothalamus (AHA), ventral medial hypothalamus (VMH), and the periaqueductal gray region (PAG) (Wood and Newman, 1995; Delville et al., 2000; **Figure 5(a)**). This pathway has been referred to as a social behavior network (Newman, 1999; Goodson, 2005), and it has also been hypothesized that different subnuclei are more active in different contexts. For example, the posteroventral MEA and dorsomedial VMH are thought to be more important for regulating aggression in defensive contexts, whereas the posterodorsal MEA and ventrolateral VMH are thought to be more important in offensive contexts (Swanson, 2000). The components of this network have been identified over the years through increasingly precise experimental methods. The involvement of the LAS, BNST, AHA, VMH, and MEA in aggression was first established through lesion studies (Miczek et al., 1974; Annen and Fujita, 1985; Kruk, 1991; **Figure 5(a)**). Next, the use of electrical stimulation of specific brain regions was found to induce aggressive behavior in regions such as the AHA (Kruk et al., 1984; Kruk, 2014). Both lesions and electrical stimulation can activate fibers of passage, and so local infusion of GABAergic or glutamatergic agonists and antagonists were used to examine local cell bodies (Haller et al., 1989; Roeling et al., 1993). Optogenetic stimulation of the ventrolateral VMH was also found to increase aggression in male mice (Lin et al., 2011). The applications of immunostaining for immediate early gene products such as c-fos largely confirmed that engaging in aggressive behavior increases the activity of neurons in the LAS, BNST, AHA, and MEA in both males (Kollack-Walker and Newman, 1995; Delville et al., 2000) and females (Davis and Marler, 2004; Hasen and Gammie, 2005; Gammie et al., 2007). More recently, immunostaining for phosphorylated proteins such as the transcription factor CREB has proved to be a useful complementary method for identifying changes in cellular activity in the brain following aggressive encounters (Trainor et al., 2010b; Heimovics et al., 2012). An important advantage of immediate early gene studies is the ability to identify cell types through multilabeling. For example subordinate male mice had more AVP neurons in the caudal paraventricular nucleus coexpressing fos compared to dominant mice (Ho et al., 2010). Similarly both male and female California mice had more AVP/c-fos-expressing cells in the caudal PVN following a resident–intruder test if they had previously experienced social defeat (Steinman et al., 2015). There is growing

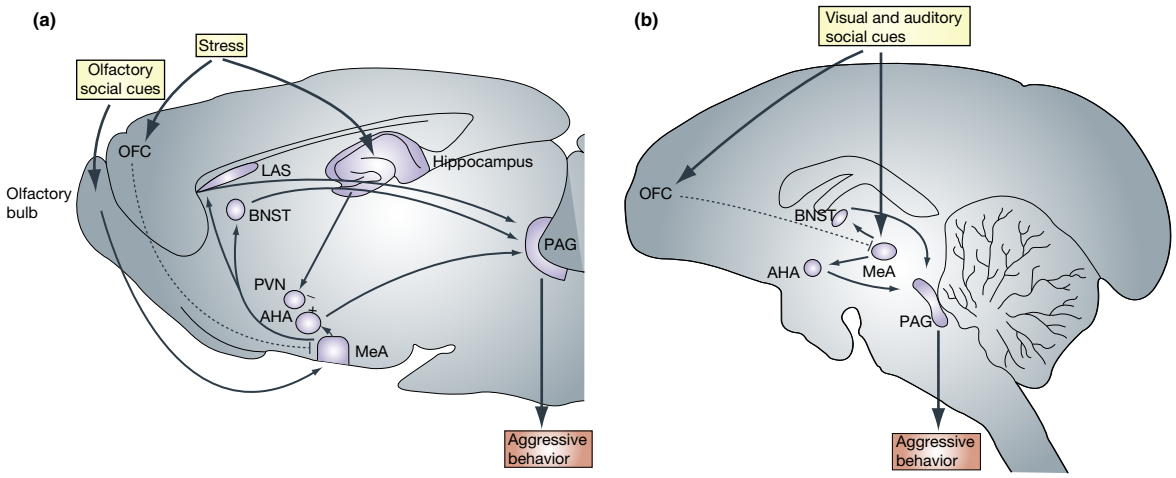

Figure 5 Neuroanatomical pathways of aggression in rodents and nonhuman primates. In rodents (a), information from the olfactory bulb is processed by the medial amygdala (MEA) and sent to the lateral septum (LAS), bed nucleus of the stria terminalis (BNST), and anterior hypothalamic area (AHA). These brain areas are thought to prompt the periaqueductal gray (PAG) into promoting species-specific aggressive behaviors. Stress can inhibit aggression via inhibitory inputs from the orbital frontal cortex (OFC), the hippocampus, and the paraventricular nucleus (PVN). In nonhuman primates (b), aggression is typically evoked by vocal or visual signals. Activation of the MEA is thought to result in activation of the BNST and AHA, which in turn activate the PAG. In general, the OFC appears to be important for the interpretation of social cues, and inhibitory inputs from the OFC might inhibit aggression by reducing responsiveness in the amygdala. Thick arrows represent inputs and outputs to and from the brain; thin arrows represent connections within the brain; dotted lines represent inhibitory connections. Reprinted from Nelson, R.J., Trainor, B.C., 2007 Neural mechanisms of aggression. Nat. Rev. Neurosci. 8, 536–546 with permission from Nature.

interest in understanding how specific cells types within the social behavior network are activated under different social contexts.

The development of viral gene transfer techniques has created new approaches for studying neural circuits of aggressive behavior. So far most studies have focused on the MEA and VMH in mice. In one study aromatase-expressing neurons in the MEA were inhibited using a designer receptor exclusively activated by designer drugs (DREADD) (Unger et al., 2015). Inhibition of MEA aromatase neurons in males increased the latency to engage in aggression without affecting the overall frequency of attacks or threats. In females inhibition of MEA aromatase neurons increased the latency and decreased the frequency of maternal aggression. The role of GABAergic and glutamatergic neurons in the MEA has been examined using optical stimulation. Activation of GABAergic neurons in the MEA was found to induce male–male aggressive behaviors while activation of glutamatergic neurons inhibited aggression (Hong et al., 2014). In the ventrolateral VMH infusion of AAV expressing small hairpin RNAs targeting ERα reduced male–male aggressive behavior (Sano et al., 2013). Intriguingly optical stimulation of ERα neurons increased male aggression directed toward both male and female intruders (Lee et al., 2014). Overall the results of experiments using modern genetic approaches are largely consistent with original reports while adding a new layer of understanding of how specific cell types control behavior.

1.05.4.2 Nonhuman Primates and Humans

As in rodents, the hypothalamus seems to play a key role in regulating aggression in nonhuman primates (**Figure 5(b)**). Electrical stimulation of the ventromedial hypothalamus increases vocal threats and piloerection in male marmosets, *Callithrix jacchus* (Lipp and Hunsperger, 1978). Similarly, lesions of the AHA and POA reduce vocal threats toward an intruder in male *C. jacchus* (Dixson and Lloyd, 1988). In rhesus monkeys (*Macaca mulatta*), electrical stimulation of the AHA, BNST, or POA increases the frequency of aggressive vocalizations (Robinson, 1967) and aggression toward subordinate males (Alexander and Perachio, 1973).

Other studies have focused on the amygdala and orbital frontal cortex (OFC). Lesions of the amygdala either increase (Machado and Bachevalier, 2006) or decrease intermale aggression (Emery et al., 2001) in rhesus monkeys. One explanation for these conflicting results is that studies that reported increased aggression reintroduced lesioned monkeys into groups, whereas studies that reported decreased aggression tested monkeys in groups of two (Emery et al., 2001), which might be less threatening. Lesions of the OFC are generally associated with reduced affiliative behavior such as grooming or close contact (Butter et al., 1970; Machado and Bachevalier, 2006), whereas their effects on aggressive behavior depend on context. For example, OFC lesions produce increased aggression in dominant, but not subordinate males (Machado and Bachevalier, 2006). In a different study, OFC lesions in dominant animals led to an initial increase in aggression that disappeared after several months (Butter and Snyder, 1972). In general, it seems that the OFC is important for the interpretation of social cues and contributes to appropriate behavioral responses in complex social situations.

A creative study used positron emission tomographic imaging to examine brain activity in rhesus macaques in the context of mate competition (Rilling et al., 2004). Dominant male monkeys witnessed a potential sexual interaction between a female they had been previously paired with and a subordinate male. This mate competition 'challenge' condition was designed to model aspects of jealousy in humans. Males exposed to this 'challenge' condition showed increased activation in the right amygdala and right superior temporal sulcus compared to males exposed to the control condition in which the subordinate male was absent. Interestingly, similar results were observed in a functional MRI study on human participants. Brain activation was increased in the amygdala and hypothalamus when men read sentences depicting sexual infidelity compared to neutral sentences, whereas women showed increased activation in the posterior superior temporal sulcus in the same comparison (Takahashi et al., 2006). Other studies suggest that the superior temporal sulcus is activated when assessing deception (Calarge et al., 2003), trustworthiness (Winston et al., 2002), and violation of social norms (Greene et al., 2001). Thus, it appears that there are at least qualitative similarities between human and nonhuman primate circuitries that function during mate competition.

A more direct link between brain activation in humans and aggression was observed in imaging studies that reported an inverse relationship between average baseline activity in the frontal cortex and measures of reactive aggression (Raine et al., 1994; Volkow et al., 1995; Soderstrom et al., 2000;

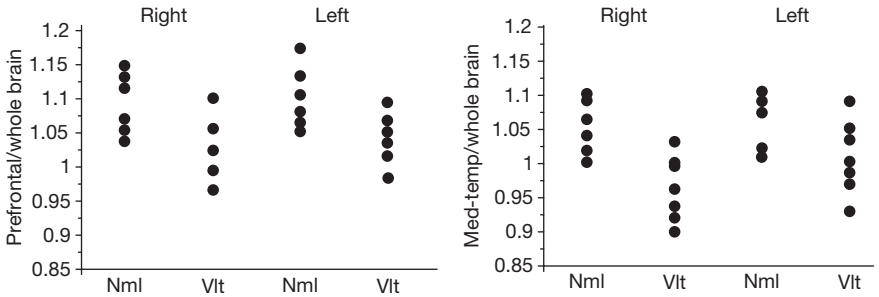

Figure 6 PET scan indicating brain changes in violent people. Individual values for relative metabolism in right and left prefrontal and medial temporal cortex of adult control volunteers (Nml) and violent patients (Vlt). Reprinted from Volkow, N.D., Tancredi, L.R., Grant, C., Gillespie, H., Valentine, A., Mullani, N., Wang, G.J., Hollister, L., 1995. Brain glucose metabolism in violent psychiatry patients: a preliminary study. Psychiatry Res. 61, 243–253, with permission from Elsevier.

Soloff et al., 2003; **Figure 6**). The frontal cortex provides inhibitory inputs to circuits in the hypothalamus and amygdala that might promote aggression (Davidson et al., 2000), although the role of these brain areas remains less well-established in humans than in other animals. In one study, individuals that had been diagnosed with intermittent explosive disorder increased activation in the amygdala in response to angry faces when compared to control participants, and amygdala activation across both groups was positively correlated with scores on the Lifetime History of Aggression (LHA) scale (Coccaro et al., 2007). Insights into brain areas that affect human aggressive behavior also come from observing the behavioral effects of brain injuries. Many studies have reported a link between brain damage to the frontal cortex and increased aggressive behavior (Grafman et al., 1996; Anderson et al., 1999). Brain injury rarely causes selective damage to the hypothalamus or amygdala. However, during a grim period in the mid-twentieth century, electrolytic lesions of these brain regions were used to treat what was deemed 'excessive aggression' (Heimburger et al., 1966; Sasano et al., 1998). Although lesions of the hypothalamus and amygdala were reported to inhibit aggression, these conclusions are limited. Measurements of behavior in these studies were usually crude and fail to account for the complexities of human behavior (Blair, 2004; Cherek et al., 2006; Scarpa and Raine, 2006; Trainor et al., 2006b). Additionally, electrolytic lesions damage fibers of passage as well as the target nuclei, and damage to the hypothalamus and amygdala affect general arousal (Tonkonogy and Geller, 1992), not just aggression. An intriguing experimental approach was developed by Carré and colleagues to examine the effects of testosterone on neural activation in response to threat-related stimuli (Goetz et al., 2014). Healthy men were given a gonadotropin-releasing hormone antagonist, which normalized T concentrations to low baseline levels. Then men were randomly assigned to be treated with T or placebo and tested in a face-matching task while undergoing fMRI. Men treated with T had greater increases in reactivity in the amygdala and hypothalamus to angry faces compared to men treated with placebo. Several studies have taken an integrative approach to studying the neurobiological circuits that influence aggression. Previous studies reported reduced activation of the prefrontal cortex in patients who were rated highly for impulsive aggression and also showed that selective serotonin reuptake inhibitors (SSRIs) reduced ratings of aggression (Coccaro and Kavoussi, 1997); the effect of SSRIs on prefrontal cortex (PFC) activity was examined in patients who had been diagnosed with borderline personality disorder (these patients score highly on measures of impulsive aggression). Twelve weeks of SSRI treatment increased baseline activation in the PFC, and PFC activation was negatively correlated with ratings of aggression (New et al., 2004). In addition, positron emission tomography (PET) imaging studies using a selective serotonin receptor type 1A (5-HT_{1A}) antagonist showed that scores on the Lifetime History of Aggression (LHA) test were negatively correlated with 5-HT_{1A} binding in the amygdala and PFC (Parsey et al., 2002; **Figure 7**). Intranasal administration of the neuropeptide hormone oxytocin to human participants reduced activation of the amygdala in response to fear-inducing pictures (e.g., sharks, snakes) (Kirsch et al., 2005). Studies in animals indicate that oxytocin can reduce aggression (Winslow and Insel, 1991; DeVries et al., 1997; Winslow et al., 2000) and that oxytocin receptors are abundant in the amygdala (Insel, 1992; Jiménez et al., 2015). Thus oxytocin might reduce human aggressive responses in some contexts, although this should be tested pharmacologically. These studies show that combining biochemical manipulations with a realistic social context can allow investigators to ethically test hypotheses that been developed using animal models.

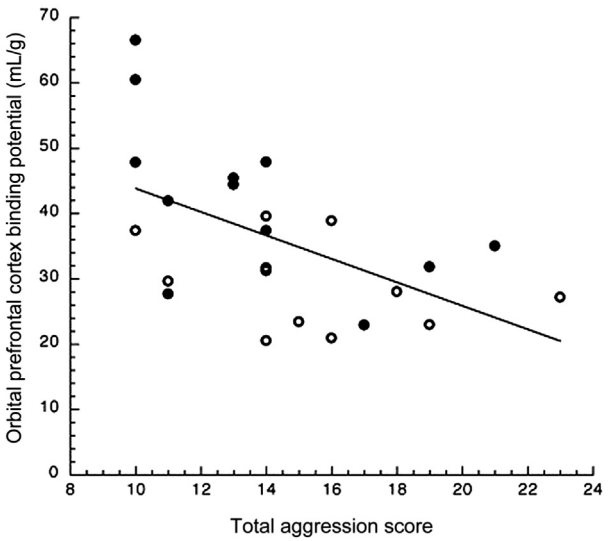

Figure 7 Inverse correlation between the binding potential in the orbital prefrontal cortex and lifetime aggression score as assessed by the Brown–Goodwin Scale. Open circles are males, filled circles are females. $R = -0.53$, $p = 0.007$ for the combined data. Reprinted from Parsey, R.V., Oquendo, M.A., Simpson, N.R., Ogden, R.T., Van Heertum, R., Arango, V., Mann, J.J., 2002. Effects of sex, age, and aggressive traits in men on brain serotonin 5-HT1A receptor binding potential measured by PET using [C-11]WAY-100635. Brain Res. 954, 173–182 with permission from Elsevier.

1.05.5 Neurotransmitters, Hormones, and Aggression

1.05.5.1 Serotonin

Serotonin is the neurotransmitter most closely associated with regulation of aggressive behavior. Nonetheless, there is no simple relationship between serotonin levels and aggressive behavior overall (Takahashi et al., 2011). More granular analyses have established both subtle and not so subtle relationships between serotonin and aggression. For example, it is now generally accepted that 5-HT_{1A} and 5-HT_{1B} receptor inhibition can reduce aggression (Morrison and Melloni, 2014), although sex differences in 5-HT_{1A} receptor activation have been observed (Joppa et al., 1997). Rats display rapidly elicited aggressive responses when an intruder is introduced into the home cage and treatment with the 5-HT_{1A} receptor agonist (8-OH-DPAT) decreases offensive aggressive behaviors in resident males (De Boer et al., 1999; De Boer and Koolhaas, 2005). However, these drugs have no effect on aggression

when administered to intruders. Additionally, highly aggressive male mice with depleted CNS 5-HT ameliorate agonistic responses after 8-OH-DPAT treatment suggesting further that the 5-HT_{1A} receptors inhibit aggressive responses.

Generally, activation of the 5-HT system dampens aggression in animals and violent behavior in humans. Impulsivity and high aggressiveness are correlated with low cerebrospinal fluid concentrations of 5-HT metabolite, 5-HIAA, in humans and nonhuman primates, and reduced 5-HT levels or turnover in the brain of laboratory animals (reviewed in Lesch and Merschdorf, 2000). Pharmacological strategies of increasing 5-HT levels such as the use of 5-HT precursors, 5-HT reuptake inhibitors, as well as 5-HT_{1A} and 5-HT_{1B} receptor agonists are able to reduce aggressive behavior in rodents (reviewed in Manuck et al., 2006). Nonetheless, in models of excessive, proactive aggression, 5-HT is unable to modulate the abnormal behavioral responses (Haller, 2013). This suggests that serotonergic mechanisms are more important for species-typical aggressive behaviors rather than models of abnormal or violent aggressive behavior.

Genetic evidence for a role of 5-HT in aggression comes from mice missing specific genes that either directly or indirectly affect 5-HT concentrations or metabolism. The 5-HT_{1B} receptor is expressed in a variety of brain regions, including the basal ganglia, periaqueductal gray, hippocampus, lateral septum, and raphe nuclei, either presynaptically inhibiting 5-HT release or as a heteroreceptor modulating the release of other neurotransmitters (Bibancos et al., 2007). Male mice that lack functional expression of the 5-HT_{1B} receptor gene (5-$HT_{1B}^{-/-}$) are more aggressive than wild-type mice (Saudou et al., 1994). Lactating female 5-$HT_{1B}^{-/-}$ mice also attack unfamiliar male mice more rapidly and violently than wild-type females (Ramboz et al., 1996). Notably, administration of the nonselective 5-HT_{1B} agonist eltoprazine (one of the so-called 'serenics') significantly reduces aggressive behavior in both 5-HT_{1B} knockout mice and WT mice, presumably by affecting 5-HT_{1A} receptors (Ramboz et al., 1996). Although the 5-HT_{1B} receptor contributes to aggression, these results suggest that the 5-HT_{1B} receptor subtype is not the sole 5-HT receptor modulating aggressive behavior. Specifically, 5-HT_{1A} receptor activation, which is also induced by eltoprazine, can also influence aggressive behaviors. Although both 5-HT_{1A} and 5-HT_{1B} receptors control the tone of 5-HT system, it seems likely that these two receptors contribute differently in particular brain areas modulating the postsynaptic 5-HT inhibitory effects on aggression (Bibancos et al., 2007). The role of other 5-HT receptor subtypes on aggression remains unspecified, but these receptors likely play a minor role (Montoya et al., 2012).

Long-term treatment with selective serotonin reuptake inhibitors (SSRIs) reduces aggression in many species ranging from fish to primates (reviewed in Morrison and Melloni, 2014). Acute SSRI treatment blocks the pro-aggressive effects of several agents such as synthetic anabolic androgenic steroids (AAS), testosterone, alcohol, and apomorphine (Morrison and Melloni, 2014). Taken together, the evidence suggests that serotonin in the CNS tends to decrease aggressive behaviors (Takahashi and Miczek, 2014). However, a recent meta-analysis of the serotonin–aggression relationship in humans only revealed a small effect size between central 5-HT and aggression, hostility, and anger (Duke et al., 2013).

Androgens, either acting directly or via estrogenic metabolites, tend to facilitate aggression, whereas increased CNS 5-HT tends to inhibit aggression. Androgens interact with 5-HT in several ways to influence aggression. For example, perinatal exposure influences the expression and distribution of 5-HT receptor subtypes (Simon et al., 1998; Sumner and Fink, 1998; Cologer-Clifford et al., 1999). Either testosterone or estradiol elevates 5-HT_{2A} receptor mRNA expression and binding site densities in male rat brains (Ferrari et al., 1999). Importantly, both androgens and estrogens modulate 5-HT_{1A} and 5-HT_{1B} receptor agonist effects on murine aggression (Simon, 2002). Thus, sex steroid hormones and 5-HT interact on several levels to influence the likelihood of aggression.

Several other classical neurotransmitters have also been linked to aggression. The most commonly related neurotransmitters associated with aggressive behaviors are discussed below.

1.05.5.2 Arginine Vasopressin

AVP is another hormone that plays a critical role in aggression and other social behaviors (Goodson and Bass, 2001; Ferris, 2006). AVP produced in the anterior hypothalamus (AH) can modulate aggression through its effects on AVP V1a receptors, 5-HT, and the serotonin receptors 5-HT_{1A} and 5-HT_{1B}. Treatment of male hamsters with a V_{1A} antagonist increases attack latencies and decreases frequency of biting in a standard resident–intruder test (Ferris et al., 2006). Interestingly, V1a antagonist infusions into the AH of female hamsters increased aggression (Gutzler et al., 2010). Somewhat consistent with this effect, V1a antagonist infused into the lateral ventricle also enhanced maternal aggression in rat dams (Nephew and Bridges, 2008). These findings indicate that the V1a receptor has very different effects on aggression in males and females.

Microinjections of AVP into the AH in combination with 5-HT_{1A} or 5-HT_{1B} receptor agonists revealed that only the 5-HT_{1A} receptor activation inhibited AVP-facilitated aggression (Ferris, 2006). 5-HT neurons project into the AH, and 5-HT appears to inhibit AVP-facilitated offensive aggression by activating 5-HT_{1A} receptors (Ferris, 2006). Several drugs that affect both AVP and the 5-HT systems reportedly reduce aggression. For example, systemic treatment of humans with nicotine increases blood AVP concentrations and central 5-HT release while reducing aggression (reviewed in Morrison and Melloni, 2014). It appears that development can impact the effects of V1a receptors on aggression. V_{1A} knockout mice have normal levels of aggression after isolation, whereas isolation of V_{1B} knockout mice reduces aggression (Wersinger et al., 2002; Morrison and Melloni, 2014). This suggests that genetic deletion of V1a results in a compensatory developmental effect in aggression circuits, possibly a greater role for V1b receptor.

1.05.5.3 Monoamine Oxidase

Metabolic enzymes such as monoamine oxidase A (MAOA) also influence aggression because they function to alter neurotransmitter concentrations. MAOA is predominantly located in catecholaminergic neurons in the brain, but MAOA catalyzes with high affinity the oxidative deamination of 5-HT,

norepinephrine, and dopamine (Shih et al., 1999). Although MAOA deficiency due to a point mutation in its coding gene is correlated with impulsive aggression in several males from a single Dutch family (Brunner et al., 1993), humans treated with pharmacological MAO inhibitors for depression generally display no change in impulsivity or aggression (Manuck et al., 2006; Buckholtz and Meyer-Lindenberg, 2008). Substantial work has related low MAOA expression with genetic factors to influence aggressive behaviors in humans (reviewed in Dorfman et al., 2014).

MAOA knockout mice display markedly increased aggressive behaviors (Cases et al., 1995; Godar et al., 2011). Ablation of the MAOA gene in mice leads to high levels of offensive aggression despite elevated 5-HT concentrations (Cases et al., 1995); the metabolic disturbances caused by MAOA deficiency throughout life likely account for the effects on aggression. Notably, the elevated aggression in humans and mice with MAOA gene disruption mostly affects males (Manuck et al., 2000; Buckholtz and Meyer-Lindenberg, 2008). MAOA activity is directly regulated by estrogen (Chakravorty and Halbreich, 1997), which may be mediated by hormone receptor response elements present in the MAOA promoter (Ou et al., 2006). In humans, environmental risk factors interact with the MAOA to produce elevated risk for aggression (Kim-Cohen et al., 2006). Interestingly, low MAOA gene expression interacts with prenatal cigarette exposure to result in elevated conduct disorder diagnoses later in life (Wakschlag et al., 2010).

1.05.5.4 Nitric Oxide

Nitric oxide (NO) was initially identified as an endogenous regulator of blood vessel tone, but is now recognized as a neurotransmitter in both the central and the peripheral nervous systems (Baranano and Snyder, 2001). Male mice with targeted deletion of the gene encoding the neuronal version of NOS (nNOS$^{-/-}$ or NOS1$^{-/-}$) displayed three to four times more aggressive behaviors than wild-type mice in the intruder–resident test (Nelson et al., 1995; Trainor et al., 2007c; Bedrosian and Nelson, 2014). Nearly 90% of the aggressive encounters were initiated by the nNOS$^{-/-}$ animals. In all test situations, male nNOS$^{-/-}$ mice rarely displayed submissive behaviors (Nelson et al., 1995). Behavioral studies of mice with targeted deletion of specific genes suffer from the criticism that the gene product is not only missing during the testing period, but also missing throughout ontogeny when critical developmental processes, including activation of compensatory mechanisms, could be affected (Nelson et al., 1997). Furthermore, differences in genetic background might also contribute to the observed changes in behavior of knockout mice (Wolfer et al., 2002). To address these criticisms, mice were treated with 7-nitroindazole (7-NI) to specifically inhibit nNOS formation *in vivo* (Demas et al., 1997). Isolated mice treated with 7-NI displayed substantially increased aggression in two different tests of aggression compared to control animals (Demas et al., 1997). The combination of the traditional pharmacological approach and a targeted gene disruption approach to studies of aggression enhances the strengths and minimizes the weaknesses of each single approach.

Plasma androgen concentrations in mice do not differ between wild types and nNOS$^{-/-}$ either before or after aggressive interactions (Nelson et al., 1995). However, castrated nNOS$^{-/-}$ mice indicate that testosterone is necessary, if not sufficient, to maintain elevated aggression in these knockout mice (Kriegsfeld et al., 1997). Androgen replacement therapy restored the elevated levels of aggression to precastration levels in both nNOS$^{-/-}$ and wild-type mice.

Serotonin function was hypothesized to be disrupted in the aggressive nNOS$^{-/-}$ mice because of the inverse relation of 5-HT system activity and aggression. Serotonin metabolism was reduced in several brain regions involved in aggression (Chiavegatto et al., 2001). Changes in 5-HT turnover were due to increased concentrations of 5-HT with no changes in its metabolite in most brain regions studied (**Figure 8**). The disturbed neurochemical profile appears specific to the 5-HT system, because norepinephrine, dopamine, and metabolites were generally unaffected. As noted, monoamine oxidase has been implicated in aggression; however, the relatively normal norepinephrine and dopamine values suggest that it is unlikely that alterations in monoamine oxidase account for the 5-HT abnormalities in the nNOS knockout mice (Chiavegatto et al., 2001).

Gonadal hormones directly influence the expression of nNOS in many regions within the hypothalamus and limbic system (Panzica et al., 2006). The effects of sex steroid hormones have primarily been achieved after medium- or long-term treatments. However, significant changes occur in particular physiological conditions, for example, during the estrous cycle. Changes are not uniform throughout the brain, but vary in specific directions in different populations of neurons (Panzica et al., 2006). Estradiol treatment seems to increase nNOS activity in the ventrolateral nucleus of guinea pigs (Warembourg et al., 1999) and in PVN (Sanchez et al., 1998) and MPA (Okamura et al., 1994) of rats. These discrepancies in the effects of gonadal hormones on nNOS

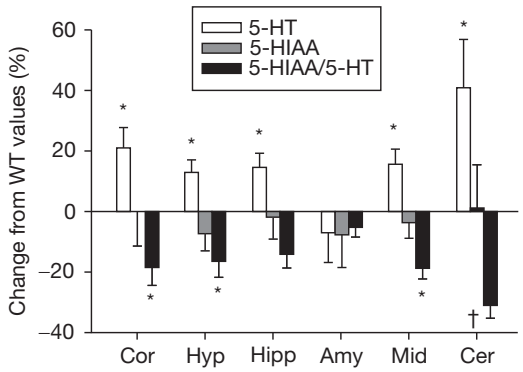

Figure 8 Serotonin (5-HT), 5-HIAA, and 5-HT turnover (5-HIAA/5-HT) ratios are reduced in mice lacking the gene for nNOS. Determination of 5-HIAA/5-HT ratio was made by HPLC in the cerebral cortex (Cor), hypothalamus (Hyp), hippocampus (Hipp), amygdala (Amy), midbrain (Mid), and cerebellum (Cer) of nNOS$^{-/-}$ as compared to WT mice. Data are percent change in relation to WT mice SEM; $^{*}p < 0.05$. Reproduced from Chiavegatto, S., Dawson, V.L., Mamounas, L.A., Koliatsos, V.E., Dawson, T.M., Nelson, R.J., 2001. Brain serotonin dysfunction accounts for aggression in male mice lacking neuronal nitric oxide synthase. Proc. Natl. Acad. Sci. U.S.A. 98, 1277–1281 with permission from the National Academy of Sciences.

could reflect a combination of factors including species differences, methodology, regional specificity, or assays of mRNA compared to protein (Panzica et al., 2006). Further work is necessary to understand the relationship among sex steroid hormones, 5-HT, and NO in mediating aggression. Additional work is necessary to understand the relationship among sex steroid hormones, 5-HT, and NO in mediating aggression.

Interestingly the effects of nNOS on aggression are mediated by the social environment. Initial studies examining effects of nNOS inactivation on aggression were conducted on singly housed males. Effects of nNOS inactivation through gene knockout or inhibition with 3BrN were blunted in males that were housed in pairs (Trainor et al., 2007c). Thus the effects of nNOS on aggression are dependent on the social environment. Social isolation decreases 5-HT_{1A} receptors (Rilke et al., 1998) and increases V1a receptors (Albers et al., 2006), which could potentially mediate the impact of nNOS on aggression. Interestingly nNOS inactivation reduced motivation to approach unfamiliar individuals or social odors. The combination of increased aggression and reduced social interaction has also been observed in rhesus monkeys with the low activity form of the serotonin transporter promoter and raised in peer-only groups. In monkeys raised by their mothers, no differences between serotonin transporter genotypes were observed (Barr et al., 2003).

Two recent studies implicate a role of NO in human aggression as well. For example, a NOS1 promoter repeat length variation (NOS1 Ex1f variable number tandem repeat (VNTR)) was identified, and the short repeat variant is associated more frequently with adult ADHD, personality disorder, and aggression. The short variants lead to reduced transcriptional activity of the NOS1 exon 1f promoter (Reif et al., 2009). Adverse environmental stressors can interact with the short variant to promote elevated impulsive behaviors, including impulsive aggressive behavior, in children aged 9–18 (Reif et al., 2011). Taken together, these studies suggest a role of NO in mediation of human impulsive aggression.

1.05.6 Development of Aggression

1.05.6.1 Rough-and-Tumble Play as an Antecedent to Aggressive Behavior

Juveniles of most species engage in agonistic behaviors that at least superficially resemble adult aggression. These behaviors are referred to as rough-and-tumble play or play fighting. In common with adult aggression, juvenile rough-and-tumble play comprises both offensive and defensive maneuvers in which animals attack, bite, pin, wrestle, roll over, and flee. Unlike adult aggression, juvenile rough-and-tumble play does not involve competition for resources, territory, or mates. In most species, including humans, juvenile males engage in more rough-and-tumble play than females. Rough-and-tumble play predominates during social interactions in prepubertal and juvenile animals and gradually declines over the course of pubertal maturation. In general, overt aggression is relatively uncommon prepubertally and increases concomitantly with reproductive maturation and the associated rise in circulating concentrations of gonadal steroids.

The gradual replacement of play fighting by 'serious' fighting over the course of ontogeny, coupled with the male bias in rough-and-tumble play, invites the conclusion that play fighting and adult fighting are a developmental continuum in which play fighting is the immature form of adult aggression. However, based on several lines of evidence gleaned primarily from studies in rats and hamsters, Pellis and colleagues contend that play fighting and adult aggression are distinct behaviors, and that play fighting is not practice for adult fighting skills, but instead is practice for general social skills and competence (Pellis and Pellis, 1988, 1997, 1998, 2007). First, play fighting and adult fighting have different topographies. In play fighting, attacks are initiated toward the head and nape, whereas in serious fighting, attacks are initiated toward the rump (Pellis and Pellis, 1988; Wommack et al., 2003; Taravosh-Lahn and Delville, 2004). Defensive maneuvers during play and adult fighting differ as well. To evade an attack, juvenile male rats rotate their bodies fully to a supine position, but adults rotate only partially so that their hind feet remain on the ground (Pellis, 2002). Play fighting is also characterized by frequent role reversals; for example, the chasee may suddenly turn around and become the chaser, or a larger animal may voluntarily self-handicap, letting a smaller animal pin or chase the larger one (reviewed in Pellis and Pellis, 2007). Such role reversals are uncommon in adult aggression. Furthermore, infant (preweaning) rats display adultlike defensive tactics, which are then replaced by the juvenile tactics (Pellis and Pellis, 1997). Thus, it does not appear that the specific motor patterns of juvenile play fighting are immature or simpler forms of adult fighting. Second, although the frequency of play fighting decreases over the course of pubertal maturation, play fighting is not unique to the juvenile period, and both play fighting and adult fighting can and do occur in adulthood (Pellis and Pellis, 1988). When play fighting occurs among adult animals, however, it is more likely to escalate to adult fighting, presumably because the adults have decreased tolerance for one another (Pellis and Pellis, 1988). Third, play fighting and adult fighting appear to have opposite valences. In anticipation of play and during play, rats emit 50 kHz ultrasonic vocalizations, which are associated with rewarding stimuli and positive social affect. In contrast, during threatening situations, including intermale fighting, rats emit 22 kHz vocalizations, which are associated with aversive stimuli and negative social affect (Knutson et al., 1998; reviewed in Knutson et al., 2002). Thus, play fighting and adult aggression appear to involve different psychological states. Fourth, neurochemical correlates of male rat juvenile play and adult aggression are not identical. Specifically, juvenile play is associated with a decrease in hypothalamic levels of cholecystokinin (CCK), whereas submission during adult aggressive encounters is not (Burgdorf et al., 2006). This finding supports the notion that juvenile play has positive valence in light of the fact that elevated levels of CCK in cortex are associated with submissive behavior during adult aggression and negative affective states (Knutson et al., 2002; Panksepp et al., 2004). Finally, opportunities to engage in rough-and-tumble play during the juvenile period appear to facilitate development of social skills and competency and, if anything, lead to reduced overt aggressive encounters in adulthood (Pellis and Pellis, 2007; Cooke and Shukla, 2011;

Panksepp and Scott, 2012). For example, play-deprived adult rats do not appear to have learned the behavioral strategies that signal submission to a dominant rat, and this lack of social competency only invites more aggression (Von Frijtag et al., 2002). Together, these lines of evidence do not support the idea that play fighting is a practice for adult aggression.

The relationship between play fighting and adult aggression is viewed differently by Delville and colleagues, who maintain that they are the same behaviors expressed during different stages of development (Delville et al., 2003; Cervantes et al., 2007; Wommack and Delville, 2007). Based on their extensive studies on the development of aggression in Syrian hamsters, they argue that play fighting attacks are similar to adult attacks in intent, even though the body part that is the target of the attack is different at the two ages (head vs rear), because both juveniles and adults flank mark during agonistic interactions as a means of communicating dominant/subordinate status. Furthermore, because the selective serotonin reuptake inhibitor fluoxetine inhibits both juvenile play fighting and adult aggression, there appears to be a common underlying neurobiology (Delville et al., 2003). The key to resolving these opposing viewpoints about whether play fighting is an immature form of adult aggression may lie in the different methodologies used to evaluate agonistic interactions. Pellis and colleagues have studied play fighting almost exclusively among group-housed siblings or familiar males in familiar environments, whereas Delville and colleagues have studied play fighting almost exclusively using a resident–intruder paradigm in which the resident has been socially isolated since weaning and the intruder is a younger and smaller animal. The latter conditions create competition and favor aggressive responses by an advantaged resident. Therefore, agonistic interactions between juvenile males under these circumstances may in fact be adultlike aggression in defense of territory, despite the animal's young age and immature reproductive status, and different topography of aggressive behavior. Thus, the distinction between play fighting and adult fighting may not rest so much on the age of the animal as it does on whether or not stakes are involved.

As a case in point, sibling rivalry between spotted hyena cub twins involves overt aggression and can result in siblicide (Frank et al., 1991; Wahaj et al., 2007). Sibling aggression within the first year of life in hyenas establishes a rank relationship within the litter and is primarily over competition for milk and food. Sibling aggression is more intense when local prey is scarce and tends to be higher within litters of low-ranking females, who are disadvantaged for access to resources within the clan (Wahaj and Holekamp, 2006). Thus, siblicide in hyenas is not obligate, as once proposed, but instead is relatively uncommon and facultative, occurring when maternal resources are insufficient to sustain two cubs (Smale et al., 1999). This example reinforces the idea that the distinction between play fighting and aggression is not age per se, but rather whether competition for resources is involved.

1.05.6.2 Endocrine Contributions to the Development of Aggressive Behavior: Perinatal Organizational Effects

Given that levels of both play fighting and adult aggression are higher in males than in females of most species, numerous investigations have examined the role of gonadal steroids in the sexual differentiation of these behaviors. Overall, sexual differentiation of play fighting conforms to the classical model in which the presence of testosterone prenatally (nonhuman primates) or during the first few days after birth (rodents) masculinizes play fighting, and in the absence of testosterone or in the presence or absence of the ovaries, a female-typical level of play fighting is observed (reviewed in Wallen, 1996; Pellis, 2002; Cooke and Shukla, 2011). In addition, human females with congenital adrenal hyperplasia, who experience relatively high levels of adrenal androgens *in utero*, display higher levels of rough-and-tumble play and 'tomboyism' relative to unaffected siblings (reviewed in Collaer and Hines, 1995).

Perinatal masculinization of play behavior most likely involves activation of both androgen and estrogen receptors in the nervous system. The androgen receptor blocker flutamide disrupts masculinization of play behavior, either when given to rat dams during the last half of pregnancy (Casto et al., 2003) or when given to male pups over the first 10 days of life (Meaney et al., 1983). Other experiments provide evidence that perinatal estrogen receptor activation also contributes to the masculinization of play behavior. Two of these experiments investigated play fighting in *tfm* rats, in which a mutation in the androgen receptor gene renders the receptor protein nonfunctional and the rats androgen-insensitive. Therefore, effects of testosterone, which is synthesized and secreted by *Tfm* rats, are presumably due to estrogen receptor activation after aromatization of testosterone to estradiol. The two investigations of play fighting in *tfm* rats are somewhat contradictory. One of them reports similar levels of play fighting in *tfm* and wild-type male rats, suggesting that estrogen receptor-mediated mechanisms are sufficient to masculinize the behavior (Field et al., 2006). The other one reports that levels of play fighting are less in *tfm* than in wild-type males, supporting a role for androgen receptor-mediated mechanisms (Meaney et al., 1983). However, play behavior was measured in different social contexts in the two studies, and while this may make the results not directly comparable, together they implicate both androgenic and estrogenic action in the sexual differentiation of play behavior.

Hormone-mediated masculinization of play behavior may involve pathways apart from the classical mechanism of hormone activation of its cognate receptor. The first of these is ligand-independent activation of the estrogen receptor. Administration of a dopamine D1 receptor agonist to neonatal female rats masculinizes their play fighting behavior, and this effect can be blocked by prior treatment with the estrogen receptor antagonist tamoxifen (Olesen et al., 2005). The second of these involves epigenetic regulation of gene transcription, specifically DNA methylation and repression of gene expression in the amygdala. Testosterone delivered directly to the amygdala of neonatal female rats is sufficient to induce male-typical levels of play fighting (Meaney and McEwen, 1986), suggesting that testosterone or a biologically active metabolite acts within the amygdala to organize sex differences in play behavior. If the methyl-binding protein MeCP2 is silenced within the amygdala of newborn male rats, juvenile play fighting is reduced to female-typical levels (Kurian et al., 2008); this effect on behavior is similar to what one would predict if testosterone action within the amygdala of newborn

males were blocked. Overall, it appears that sexual differentiation of play fighting involves multiple hormones and multiple mechanisms.

Similar principles apply to the perinatal sexual differentiation of adult aggression. That is, the transient elevation in testosterone in male neonates leads to higher levels of aggression in adulthood (compared with females), and surgical or pharmacological castration of neonatal males leads to reduced levels of aggression in adulthood (Bronson and Desjardins, 1969). Conversely, treatment of neonatal females with testosterone masculinizes their levels of adult aggression (Bronson and Desjardins, 1970). Prenatal androgens also appear to masculinize aggression in humans, as a study found that girls with CAH are not only rated as more aggressive than unaffected girls, but also are as aggressive as boys. A fascinating variation on this theme occurs in spotted hyenas, in which higher social rank of females within the clan is associated with higher maternal androgens during late gestation (Dloniak et al., 2006). These higher gestational concentrations of androgen lead to higher levels of aggression in the offspring. Thus, maternal androgens not only organize aggressive behavior, but they also are a mechanism through which social status traits are epigenetically transferred from mother to daughter.

At least some of the masculinizing effects of perinatal testosterone on adult aggression are due to estrogenic action (Martinez-Sanchis et al., 1996). As described elsewhere in this chapter, males have both an androgen and an estrogen-sensitive circuitry that underlies hormone-facilitated aggression. Work by Simon and colleagues in mice has demonstrated that estradiol, presumably derived from aromatized testosterone, masculinizes the estrogen-sensitive circuit, while masculinization of the androgen-sensitive circuit is due to direct androgenic action during early postnatal development (Martinez-Sanchis et al., 1996).

1.05.6.3 Endocrine Contributions to the Development of Aggressive Behavior: Pubertal Organizational Effects

Another period of hormone-dependent organization of social behaviors, including aggression, occurs during puberty, when testicular hormone concentrations are once again elevated in males and when ovarian hormone cycles commence in females (reviewed in Schulz et al., 2009). An organizational role for pubertal hormones has been demonstrated by experiments in which gonadectomy performed after the perinatal period of sexual differentiation but before the onset of puberty results in long-lasting alterations in agonistic interactions. Prepubertal castration prevents the normal transition from complete to partial rotations in male play fighting defensive behaviors. Interestingly, ovarian hormones appear to suppress in females the pubertal emergence of a male-typical increase in roughness of play fighting (Pellis, 2002).

Testicular hormones during puberty program agonistic behaviors in adult hamsters. One agonistic behavior commonly observed in male–male encounters is flank marking, in which flank gland secretions are rubbed onto objects in the environment as a means of communicating dominant/subordinate status. Male hamsters initially use overt aggression and submission to quickly establish a dominant–subordinate relationship. In subsequent encounters, aggressive and submissive behaviors decline. These behaviors are replaced by flank marking as a means to more peacefully maintain the relationship. If male hamsters are castrated prepubertally, then testosterone replacement in adulthood fails to activate flank marking behavior, as it normally does if hormone replacement is given to hamsters that are castrated in adulthood (Schulz et al., 2006). Furthermore, male hamsters deprived of testosterone during puberty fail to replace overt aggression with flank marking and resort to fighting again when reintroduced to each other after having established a dominant–subordinate relationship during earlier encounters (De Lorme and Sisk, 2013). Similarly, territorial scent marking in tree shrews is organized by the pubertal rise in testosterone, since castration prior to puberty prevents activation of this behavior by testosterone in adulthood (Eichmann and Holst, 1999).

Testicular hormones during puberty also program the level of aggression displayed by adult hamsters. In one study (Schulz et al., 2006), males were castrated either before or after puberty, and then 6 weeks later were treated with either vehicle or testosterone. One week after hormone replacement, agonistic behaviors were assessed in a resident–intruder test (**Figure 9**).

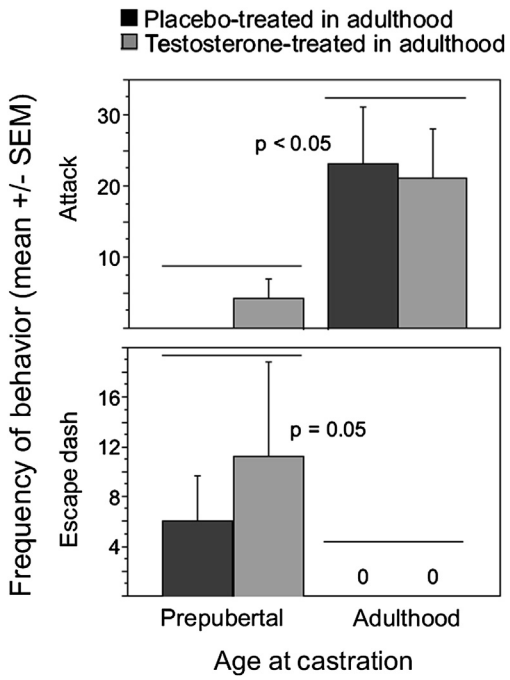

Figure 9 Aggressive and submissive behaviors expressed by male Syrian hamsters in a 10-min resident–intruder test. Subjects were castrated either prepubertally or in adulthood, and 6 weeks later treated for 1 week with either placebo or testosterone. When endogenous testosterone was absent during adolescent development (prepubertal castration group), behavior in adulthood was characterized by fewer attacks and more escapes compared to when endogenous testosterone was present during adolescent development. Thus, testicular hormones, acting during puberty, program higher levels of aggression in adulthood, even though testosterone does not exert activational effects on these behaviors in adulthood in this species. Reprinted from Schulz, K.M., Sisk, C.L., 2006. Pubertal hormones, the adolescent brain, and the maturation of social behaviors: lessons from the Syrian hamster. Mol. Cellular Endocrinol. 254–255, 120–126, with permission from Elsevier.

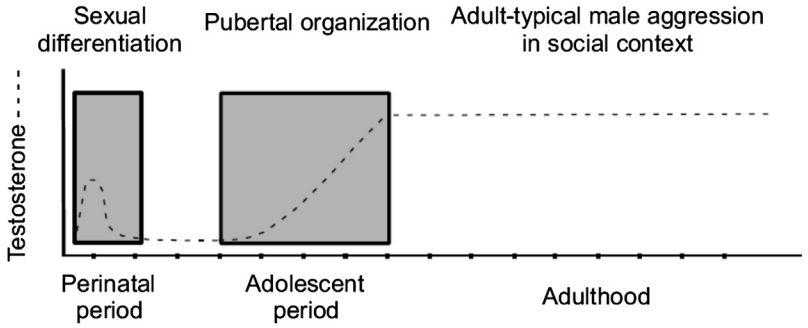

Figure 10 Aggressive and submissive behaviors expressed by male Syrian hamsters in a 10-min resident–intruder test. Subjects were castrated either prepubertally or in adulthood, and 6 weeks later treated for 1 week with either placebo or testosterone. When endogenous testosterone was absent during adolescent development (prepubertal castration group), behavior in adulthood was characterized by fewer attacks and more escapes compared to when endogenous testosterone was present during adolescent development. Thus, testicular hormones, acting during puberty, program higher levels of aggression in adulthood, even though testosterone does not exert activational effects on these behaviors in adulthood in this species. Reproduced from Schulz, K.M., Sisk, C.L., 2006. Pubertal hormones, the adolescent brain, and the maturation of social behaviors: lessons from the Syrian hamster. Mol. Cellular Endocrinol. 254–255, 120–126, with permission from Elsevier

Irrespective of testosterone or vehicle treatment in adulthood, males castrated prior to puberty did not attack the intruder and displayed high levels of submissive behaviors. In contrast, males that were castrated after puberty attacked the intruder and rarely displayed submissive behaviors. Organizational effects of adolescent hormones on male aggression have also been reported in other species, as evidenced by long-lasting changes in aggressive behavior when hormones are manipulated during the pubertal period. Male DBA/1Bg mice are normally very aggressive, but the absence of gonadal hormones during adolescence prevents activation of aggressive behavior by testosterone in adulthood (Shrenker et al., 1985). Similarly, adult testosterone treatment only partially restores aggressive behavior in prepubertally castrated male gerbils (Lumia et al., 1977), indicating that pubertal hormones program behavioral responses to hormones in adulthood.

Agonistic behaviors in female rodents may also be organized during adolescence. If female mice are ovariectomized at the onset of puberty (30 days of age), treated with testosterone for 3 weeks during adolescent development, and then tested 6 weeks after discontinuation of testosterone treatment, the levels of aggressive behavior toward another female in a neutral arena are much higher than in females treated with vehicle (Edwards, 1970). Thus, adolescent exposure to androgen has long-term effects on aggression in female mice, and the nervous system remains sensitive to organizing influences of gonadal steroid hormones well into postnatal life. However, the adolescent brain appears to be less sensitive than the neonatal brain to organizational effects because more testosterone and longer duration of treatment are required to masculinize aggression during puberty than on PND1.

Overall, sexual differentiation of play fighting and adult aggression is a two-stage process involving gonadal hormone action in the nervous system during perinatal and pubertal periods of development. Perinatally, testicular hormones, via both androgenic and estrogenic action, drive the initial masculinization and defeminization of circuits underlying juvenile play and adult aggression. Pubertally, both testicular and ovarian hormones reinforce and refine the sexual differentiation of neural circuits to result in sex-typical expression of aggressive behavior in adulthood (Figure 10).

1.05.6.4 Endocrine Contributions to the Development of Aggressive Behavior: Pubertal Activational Effects

Generally speaking, levels of aggression increase over the course of puberty as an animal achieves reproductive fertility and faces the responsibility of obtaining its own food and shelter, fending for itself, finding a mate, and potentially caring for offspring. Because the pubertal increase in aggression temporally coincides with the pubertal rise in gonadal and adrenal steroid hormones, it is logical to conclude that pubertal hormones activate the behavior in particular social contexts. Indeed, as detailed above, there is strong evidence for androgenic and estrogenic activation of adult aggressive behavior in many rodent species, with the caveats that the causal relationship between hormones and aggression is often a two-way street, and that effects of hormones on aggression are modulated by genetic background, experience, and complex interactions between the two. Evidence for activational effects of hormones on aggression in adulthood notwithstanding, the expression of agonistic behaviors over ontogeny is not governed by hormones in all cases. Play fighting during the prepubertal and juvenile periods of life is clearly not under gonadal hormone control, because hormone levels are at their nadir at this point in development. However, during early puberty, initiation of play is activated by testicular hormones, as evidenced by a reduction in play in male rats gonadectomized just prior to puberty (Cooke and Woolley, 2009). In Syrian hamsters, pubertal increases in intermale aggression proceed similarly in both gonad-intact males and males castrated a few days after weaning (Whitsett and Vanderbergh, 1975). Thus, the pubertal increase in testosterone is not an absolute requirement for the expression of adult aggression.

Normal pubertal changes in play fighting involve both androgen and estrogen receptor-mediated processes as revealed by an examination of play fighting in *tfm* rats. *Tfm* rats do not show the typical decrease in play fighting with age and are more likely than wild-type rats to show the juvenile-typical defensive

complete rotation in adulthood (Field et al., 2006). On the other hand, *tfm* males do show normal age-related changes in the use of partial rotations and upright postures. Thus, functional androgen receptors appear to be necessary for some, but not all, developmental changes in the quantity and quality of play fighting. The transition from play fighting (attacks toward head) to adult aggression (attacks toward rear) in hamsters appears to be due to increasing corticosteroid concentrations during puberty (Wommack and Delville, 2007).

1.05.6.5 Social Experience and the Development of Aggressive Behavior

In both humans and animals, early life social experience and opportunities for juvenile play fighting influence the expression of aggression in adulthood (reviewed in Cooke and Shukla, 2011; Veenema, 2012; Haller et al., 2014). For example, male rats that are singly housed from 3 to 5 weeks of age (during the prepubertal/adolescent period) show less submissive behavior during territorial aggression by a resident male compared with rats that are group-housed during adolescence (van den Berg et al., 1999). Similarly, isolation rearing from 3 to 7 weeks of age leads to increased shock-induced defensive aggression, an effect that is ameliorated by daily play fighting experience during the period of social isolation (Potegal and Einon, 1989). Thus, social interactions in the form of juvenile play appear to buffer against heightened aggression in response to provocation.

Research using the Syrian hamster to examine the effects of social subjugation on subsequent expression of aggression illustrates the importance of two types of interaction that influence the development of aggressive behavior. First is the interaction between social experience and context. If prepubertal male hamsters are socially subjugated by experiencing repeated defeat in male–male social encounters, then they subsequently show enhanced aggression toward a smaller and younger intruder, whereas they show reduced offensive responses toward an intruder of similar age and size (Delville et al., 1998). Thus, subjugation can lead to heightened or reduced aggression, depending on social context. Prepubertal subjugation also accelerates the transition from play fighting to adult aggression and increases aggression in adulthood, which may be mediated by an increase in adrenal glucocorticoid secretion brought about by the stress of defeat (Wommack et al., 2003). Second, the effect of subjugation on aggression depends on the age at which subjugation occurs. In contrast to prepubertal subjugation, subjugation in adulthood leads to complete suppression of aggressive behavior in male hamsters, a phenomenon known as conditioned defeat (see below Huhman et al., 2003). Subjugation of hamsters after mid-puberty leads to an adult-typical response to subjugation, i.e., decreased aggression toward an intruder (Delville et al., 2003), suggesting that the developmental switch responsible for the different responses to subjugation observed in juvenile and adult hamsters occurs shortly after the pubertal rise in testosterone. However, it is not clear that testosterone either triggers the switch or is part of the switch, because as described above, the absence of testicular hormones during adolescent brain development renders male hamsters less aggressive and more submissive during male–male encounters (Schulz et al., 2006). This finding does not easily lead to the prediction that the presence of testicular hormones during adolescence would result in conditioned defeat responses to subjugation.

1.05.6.6 Conditioned Defeat

After defeat in the home cage of an aggressive conspecific, male hamsters (*Mesocricetus auratus*) will subsequently fail to defend their home territory even if the intruder is a smaller, nonaggressive male (Huhman et al., 2003). This phenomenon has been called conditioned defeat and appears to evoke a stress response via fear conditioning (Huhman and Jasnow, 2005). The physiological effects of defeat include elevated HPA axis activity such as increased plasma ACTH, β-endorphin, cortisol, and corticosterone concentrations, as well as decreased plasma testosterone and prolactin concentrations (Huhman et al., 1990, 1991). This endocrine profile is observed among previously defeated hamsters upon reexposure to another animal – even when the new opponent is blocked by a physical barrier (Huhman et al., 1992). This latter response suggests that this change in endocrine profile is in response to a psychological stressor and not to the pain or anxiety of the combat itself. Social defeat also affects immune responses (Fleshner et al., 1989; Jasnow et al., 2001). The physiological and behavioral consequences of conditioned social defeat persist for at least 33 days (Huhman et al., 2003), and perhaps throughout adulthood (Delville et al., 1998). Few female hamsters exhibit conditioned social defeat, although ACTH concentrations were reduced in those females that displayed low levels of submissive/defensive behavior (Huhman et al., 2003). In contrast to males, the conditioned defeat response did not persist beyond the first test among female hamsters. These results suggest that in male hamsters conditioned defeat is a profound, persistent behavioral change characterized by a total absence of territorial aggression and by the frequent display of submissive and defensive behaviors (Huhman and Jasnow, 2005).

1.05.6.7 Aggression in Aged Individuals

At the other end of the life span, heightened aggressive and sexually offending behaviors by aged individuals can pose difficulties for themselves, their caretakers, family members, and fellow elderly residents living in assisted care facilities (Pulsford and Duxbury, 2006). Some clinical studies have assessed hostility as a 'proxy' for human aggression. Despite its imprecision, hostility has proven to be a useful construct in studies of the influences of hormones among aggressive elderly people. For example, postmenopausal women using HRT scored lower on hostility scales than women that did not use HRT (Steffen et al., 1999; Olson et al., 2004). These reports suggest estrogens can influence the expression of aggressive behavior. Studies of men and women who have been diagnosed with dementia and display physical or verbal aggression suggest a positive correlation with circulating testosterone and a negative correlation with circulating estradiol (Orengo et al., 2002). Treatment of patients with dementia with estrogens reduced aggression and sexually offending behaviors (Kyomen et al., 1991, 1999). Despite the significant problems associated with heightened aggression among some elderly patients, especially those

with moderate-to-severe dementia, there has been remarkably little animal research on this topic. Mice with mutated human amyloid precursor protein (APP) and presenilin (PS1) genes display shorter latencies to attack and increased numbers of attacks, suggesting that the plaques and tangles associated with dementia may contribute to aggression (Minkeviciene et al., 2004; Alexander et al., 2011).

1.05.7 Reciprocal Effects of Aggression on Steroid Hormones

Hormones influence aggressive behaviors, but it should be emphasized that aggressive behavior can feed back and affect hormone concentrations. Male mice and Syrian hamsters reduce circulating androgen concentrations if they lost a fight in paired aggressive encounters (Lloyd, 1971; Huhman and Jasnow, 2005). This endocrine suppression lasted for several days postdefeat. Similarly, rhesus monkeys that were defeated by a higher-ranking male had dramatically reduced testosterone concentrations for several weeks postdefeat. In contrast, winning males' circulating testosterone concentrations quadrupled within 24 h of victory (Bernstein et al., 1977).

1.05.7.1 Gene–Environment Interactions

Studies of aggression are typically conducted under a single set of environmental conditions. However, mechanisms of aggressive behavior have evolved in fluctuating physical and social environments. Perhaps not surprisingly, several neurochemical pathways of aggression function differently depending on the environment.

One of the most repeatable observations in studies of human aggression is the interaction between early life experience and genotype for the human MAOA gene. Caspi et al. (2003) reported that the effect of child abuse on behavior was significantly stronger if the child carried alleles associated with low MAOA activity (**Figure 11(a)**). Abused children with low MAOA activity had increased antisocial behavior, greater prevalence of conduct disorder, and a higher likelihood of convictions of violent offenses than abused children with high MAOA activity. In children who were not abused, the polymorphism had no effect on these measures of behavior. This gene–environment interaction has been replicated in some studies (Foley et al., 2004; Kim-Cohen et al., 2006), but not others (Huizinga et al., 2006; Young et al., 2006). An initial meta-analysis indicated that on average, children with genotypes for low MAOA activity have elevated rates of antisocial behavior when exposed to parental maltreatment (Kim-Cohen et al., 2006). A more recent meta-analysis of 31 studies (including both community-based and clinically referred samples) also found that the allele for low MAOA activity was significantly associated with antisocial behavior and aggression (Ficks and Waldman, 2014). However, variability in effect size was quite large across studies and this variability was not associated with sample or study characteristic. Thus it is still unclear how the environment interacts with MAOA function to modulate antisocial behavior and aggression.

There is also growing evidence that genetic variation in serotonin transporter (5-HTT) is linked to aggression and antisocial behavior. The short allele of the 5-HTT gene is associated with reduced expression of 5-HTT in the brain and inefficient reuptake of 5-HT from the synapse (Greenberg et al., 1999). The interaction between stress and 5-HTT genotype was examined in men and women who were instructed to administer shocks to a confederate as punishment for incorrect responses in a memory task (no shocks were actually delivered) (Verona et al., 2006). Half of the participants were subjected to a physical stressor (unpredictable air blasts to the throat) whereas the other half were not. Men, but not women, who were homozygous for the short allele were more likely to administer shocks under the stressed condition, whereas there were no genotype differences in the control condition. This interaction could be mediated by differences in threat perception, as individuals carrying the short allele have increased activation in the amygdala in response to fear-inducing pictures (Hariri et al., 2002). A recent meta-analysis of 18 studies also found that the short allele was significantly associated with increased antisocial behavior (Ficks and Waldman, 2014). Interestingly, there was some evidence for publication bias such that studies with smaller sample size tended to report large effect sizes. In addition, as with MAOA, there are many unanswered questions on how the environment interacts with 5-HTT function to modulate aggression.

In rodents several studies have demonstrated that parental behaviors can influence the effects of genes on aggression. Males of the NZB strain are more aggressive the CBA/H strain (Roubertoux and Carlier, 1988). If male NZB mice are crossed with females of the CBA/H strain, then the resulting male offspring are more aggressive, but only if raised by CBA/H dams. However, if hybrid pups are cross-fostered to hybrid mothers, then the pups are no more aggressive as adults than male CBA/H strains (Carlier et al., 1991). In these studies the specific differences in maternal care were not identified. More detailed studies have observed the effects of parental care on aggression in *Peromyscus*. Male *Peromyscus californicus* are more aggressive than male *Peromyscus leucopus* (Bester-Meredith et al., 1999), but if male *P. californicus* are cross-fostered to *P. leucopus* parents, then this species difference in aggression disappears (Bester-Meredith and Marler, 2001). Correlational analyses suggested that parental retrieving behavior was a critical factor (Bester-Meredith and Marler, 2003; Marler et al., 2003), and a subsequent study showed that experimentally increasing retrieval behavior in *P. californicus* increased aggression in male and female offspring (Frazier et al., 2006), possibly by inducing increased T secretion in pups (Becker et al., 2010). Interestingly, the absence of a California mouse father has a major impact on the development of aggression. Female but not male California mice raised without the father were significantly more aggressive and had reduced the sensitivity of the frontal cortex to dopamine (Bambico et al., 2015).

The context in which mice are tested can also have important effects on behavior. Male mice are usually more aggressive in resident–intruder tests, when intruders are introduced into a residents' home cage compared to neutral tests when two mice are introduced into a neutral arena. Patterns of aggression in one context do not necessarily transfer to a different context. For example, the correlation between mossy fibers in the hippocampus and aggression is positive if male mice are tested

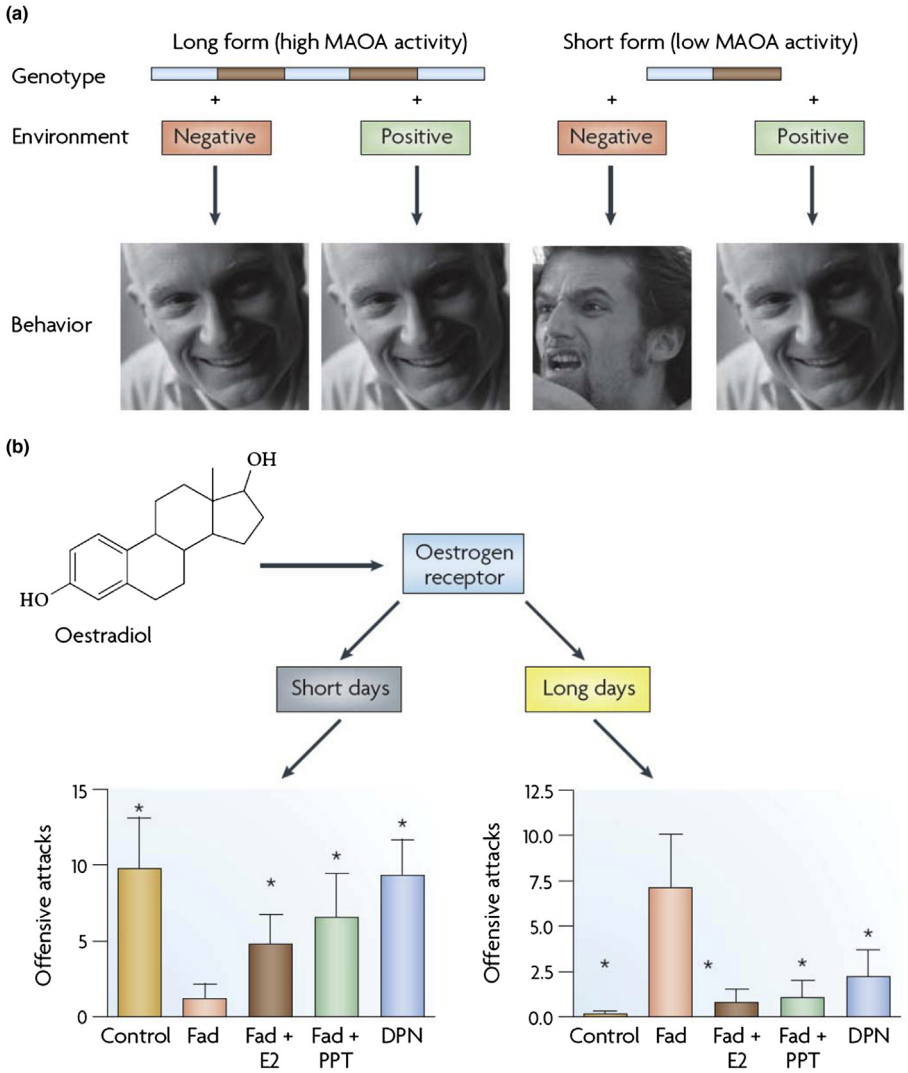

Figure 11 Gene–environment interactions in humans and mice. The interaction between the monoamine oxidase A (MAOA) genotype and the rearing environment affects aggressive behavior (a). Although they have not been replicated in every study, most data suggest that children carrying the short form of the MAOA promoter gene, which confers decreased MAOA activity, are more likely to develop conduct disorders and increased antisocial behavior when exposed to abusive home environments. This environmental effect is less prevalent in individuals carrying the long form of the promoter. Photoperiod determines the directional effects of estrogens on aggressive behavior in beach mice (*Peromyscus polionotus*) (b). *Peromyscus polionotus* are more aggressive when exposed to short days (shown in the left graph) than when exposed to long days (shown in the right graph). Treatment with the estrogen synthesis inhibitor fadrozole (fad) decreases aggression if beach mice are tested in short days, but increases aggression if tested in long days. The effects of fad are reversed with cotreatment with estradiol (E2). This does not appear to be mediated by differences in receptor expression, because the drugs PPT (propylpyrazole-triol, an estrogen receptor (ER)-α agonist) and DPN (diarylpropionitrile, an ERβ agonist) both increase aggression on short days and decrease aggression on long days. Photoperiod apparently regulates the molecular actions of estrogens, acting rapidly on short days (presumably nongenomically) and more slowly on long days (presumably genomically). Reprinted from Nelson, R.J., Trainor, B.C., 2007. Neural mechanisms of aggression. Nat. Rev. Neurosci. 8, 536–546 with permission from Nature.

in a resident–intruder test (Guillot et al., 1994), but is absent if mice are tested in a neutral arena (Roubertoux et al., 1999). It has also become clear that social status may be a critically overlooked variable in studies using domestic mice. For example, male C57 mice are typically housed four to five mice per cage. However, each cage typically has one dominant mouse that directs aggression at its cage mates (Howerton et al., 2008). This alters not only behavior, but brain circuits that modulate aggression (Greenberg et al., 2014). This is likely an important factor contributing to increased variability in neuroscience studies using male rodents compared to studies using females, even when estrous cycle is not controlled for (Prendergast et al., 2014). Finally, the outcomes of resident–intruder tests also depend on whether the intruders used are a different genotype than the test mice (Maxson et al., 1989). For example, genetic variation in the steroid sulfatase gene (*Sts*) affects male aggressive behavior when there is no risk of the opponent retaliating (such as when males are olfactory bulbectomized), but has no effect when there is a risk of injury from the opponent (Maxson et al., 2001).

In mice of the genus *Peromyscus*, photoperiod determines the mechanisms through which estrogens control male aggressive behavior (Laredo et al., 2014b; **Figure 11(b)**). Similar to hamsters, three species of *Peromyscus* are more aggressive when exposed to short days than when exposed to long days (*Peromyscus maniculatus* and *Peromyscus polionotus* (Trainor et al., 2007b); *P. californicus* (Nelson and Trainor, 2007; Trainor et al., 2007b)). In *P. polionotus*, estrogens decrease aggression when mice are housed in long days, but increase aggression if mice are housed in short days (Trainor et al., 2007a). Hormone manipulation studies showed that the ERα agonist PPT and the ERβ agonist DPN increased aggression in 'short-day' mice and decreased aggression in 'long-day' mice. These data suggested that photoperiod regulates processes that occur after estrogens bind their cognate receptors. Steroids can affect physiological and behavioral processes via genomic or nongenomic pathways (Vasudevan and Pfaff, 2006). Classical genomic action occurs when ligand-bound receptors bind to hormone response elements that facilitate transcription. This process typically takes hours or days. Nongenomic action can occur through several pathways including phosphorylation of cellular signaling pathways and changes in intracellular calcium. Nongenomic effects can occur within seconds of estrogens binding receptors. Gene chip analyses of *P. polionotus* indicated that estrogen-dependent gene expression was increased in the BNST of long-day mice compared to short-day mice, suggesting estrogens might act via nongenomic pathways in mice exposed to short days. In *P. polionotus* estradiol injections acted rapidly (15 min) to increase aggression in short-, but not long-day mice, suggesting that estradiol increases aggression via nongenomic action (Trainor et al., 2007a). This same result was also observed in *P. californicus* (Trainor et al., 2008). The rapid effects of estradiol on aggression in short-day mice were not blocked by pretreatment with a protein synthesis inhibitor, consistent with nongenomic action (Laredo et al., 2013). However, these follow-up studies identified an unexpected twist. Whether estradiol increased or decreased aggression was dependent on type of bedding used to line the cages.

In the initial studies, cages were lined with corncob bedding and estrogens increased aggression under short days (Trainor et al., 2007a, 2008). However, when a cardboard-based bedding was used, estradiol decreased aggression under short days (Laredo et al., 2013). Importantly, the rapid effects of estradiol on aggression were absent under long days. When the two beddings were directly compared, the aromatase inhibitor fadrozole increased aggression in mice housed with cardboard-based bedding and decreased aggression in mice housed with corncob bedding (**Figure 12**; Villalon Landeros et al., 2012). Mice housed on corncob bedding had elevated blood levels of tetrahydrofuran diols (THF-diols), which are estrogen-like compounds that can alter estrogen-dependent behavior such as lordosis (Markaverich et al., 2002). Corncob bedding has been found to reduce anxiety-like behavior and decrease sex differences in stress responses. Although the exact mechanism through which corncob bedding alters estrogen-dependent behaviors is unknown, one possibility is the regulation of extracellular signal regulated kinase (ERK). California mice housed on corncob bedding had greatly reduced pERK immunoreactivity in the BNST, MPOA, MEA, and VMH. The effects of bedding are significant because

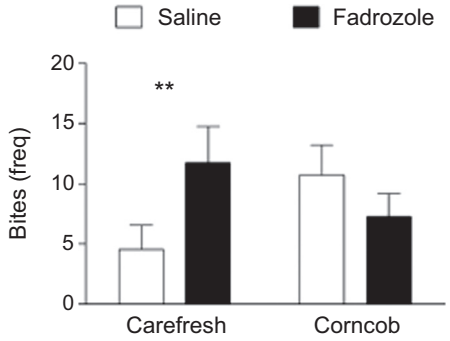

Figure 12 The effects of estrogens on aggression depend on cage bedding. Aromatase inhibition with fadrozole increased the number of bites on Carefresh bedding but not on corncob bedding. **, $P < 0.01$, planned comparison for effect of fadrozole; n = 10–14 per group. Reprinted from Villalon Landeros, R., Yoo, H.J., Morisseau, C., Fu, S., Hammock, B.D., Trainor, B.C., 2012. Corncob bedding reverses the effects of estrogens on aggressive behavior and reduces estrogen receptor alpha expression in the brain. Endocrinology 153, 949–953 with permission from the Endocrine Society.

pERK immunoreactivity in BNST and MEA is increased during resident–intruder tests when aggression is induced (Trainor et al., 2010a,b). Further study is needed to determine how environmental estrogens modulate the rapid effects of endogenous estrogens on aggression.

1.05.8 Integration

Neurochemical and neuroanatomical pathways of aggression have been investigated in various species, and it is apparent that some pathways are common to humans and nonhuman animals. Increasing serotonergic activity decreases reactive aggression in humans and also reduces aggression in a mouse resident–intruder test, probably by decreasing impulsivity. A more challenging task is determining how murine behavior in a resident–intruder test relates to reactive or instrumental aggression in humans. Aggression researchers have been struggling with this question, and a comprehensible answer has not yet emerged. This may be because there is no unambiguous answer. In humans, reactive aggression appears to be governed more by serotonergic pathways, whereas the motivated characteristics of instrumental aggression suggest a role for dopaminergic pathways. Given the enormous differences in biology and social structure, it is unlikely that mouse and human aggression can be classified into homologous categories. However, it is clear that many neurochemical systems (such as the serotonergic system) have coevolved in mice and humans to regulate species-specific aggressive behaviors. Thus, although aggressive behavior is expressed in different contexts with different behavioral outputs in mice and humans, similar neurochemical and neuroanatomical pathways are activated. Difficult questions remain to be answered. For example, to what extent does an impoverished background influence the development of these neurochemical and neuroanatomical pathways, and to what extent are they activated by observing aggression? Considerable debate ensues on the

effects of violence in the media on aggression, and myriad confounding factors make it difficult to study these putative effects. Aggression is increased in animals that observe conflicts among other individuals (Earley and Dugatkin, 2002; Peake et al., 2002). Generally overlooked by mental health researchers, these data show that vicarious experiences have important biological effects. Sports fans respond to watching their team win or lose with corresponding increases or decreases in testosterone levels (Bernhardt et al., 1998; **Figure 13**). Children playing violent video games show reduced activation of brain areas involved in affect, such as the amygdala and the anterior cingulate cortex (Mathiak and Weber, 2006). Reduced brain activity in frontal areas has also been reported in children with high exposure to violent video games and television programs (Mathews et al., 2005). Although it is not clear whether these experiences have long-term behavioral effects, it is clear that vicarious experiences have consistent short-term influences on brain activity. It is perhaps unsettling that these patterns resemble those identified in individuals with dysregulated aggression (Volkow et al., 1995; Soloff et al., 2003). Biology-based approaches to examine the effects of observing violence on aggressive behavior, if they are conducted in realistic social contexts (in addition to questionnaires and other pencil-and-paper approaches), have potential because they allow more precise measurements of the neural circuits that influence aggressive behaviors. Another issue of concern to clinicians is how to treat uncontrolled aggression. This is a complicated issue because, although it is agreed that unchecked aggression has negative consequences, a certain amount of human aggression is probably necessary to succeed in life. Clinical trials have investigated many treatments aimed at reducing elevated aggression that is associated with mental disorders, but treatments that can ameliorate excessive aggression have unwanted side effects on processes such as arousal (Cherek et al., 2006). Although further advances in drug development may lead to additional improvements in the treatment of pathological aggression, the complexity of aggressive behavior suggests that it might not be possible to control aggression. A more effective strategy for dealing with uncontrolled aggressive behavior may lie in a combination of biological and behavioral approaches, especially for instrumental aggression.

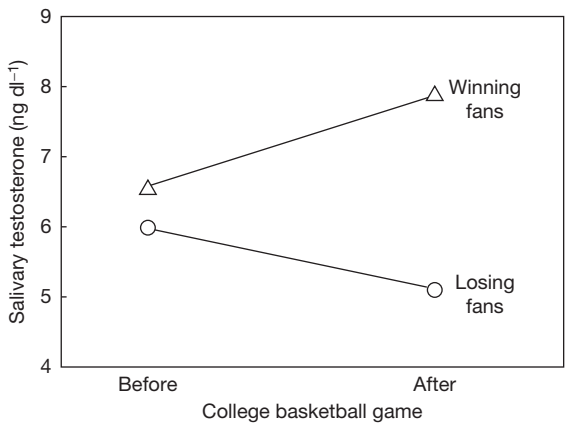

Figure 13 Basketball fans' testosterone levels before and after their team has won or lost. Reprinted from Bernhardt, P.C., Dabbs, J.M., Fielden, J.A., 1998. Testosterone changes during vicarious experiences of winning and losing among fans at sporting events. Physiol. Behavior. 65, 59–62, with permission from Elsevier.

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