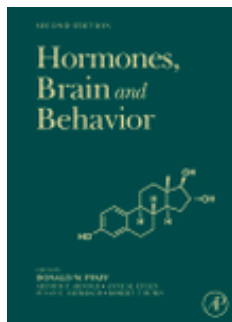


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Trainor B C, Sisk C L and Nelson R J Hormones and the Development and Expression of Aggressive Behavior. In: Donald W. Pfaff, Arthur P. Arnold, Anne M. Etgen, Susan E. Fahrbach and Robert T. Rubin, editors. *Hormones, Brain and Behavior*, 2<sup>nd</sup> edition, Vol 1. San Diego: Academic Press; 2009. pp. 167-203.

## 5 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 (HRE)** This is made up of 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.

## 5.1 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., 2007a). 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 excessive aggression remains an important, yet understudied endeavor.

One factor limiting progress is the validity of animal models of human violent behavior. For example, in studies of animal models of aggression, it is rare that normal, adaptive aggression is differentiated from pathological violence (Haller and Kruk, 2006; Miczek et al., 2007a,b; Nelson and Trainor, 2007; Sluyter et al., 2003). 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).

Thus, the neural and biological mechanisms underlying violent behavior are not well understood, although our understanding of the mechanisms underlying aggressive behavior is growing. This chapter focuses on the interaction between hormones and aggressive behaviors. For the purposes of this chapter, two broad associations suggest that hormones are involved in aggression. First, a dramatic sex difference exists in aggression and violence across species and situations: males are typically more aggressive than females. A notable exception to this bromide is that females defending their young are fiercely aggressive (Gammie et al., 2007). The extent to which human sex differences in violence are due to hormones (or other physiological differences) or reflect differences in socialization remains unspecified. Moderate testosterone concentrations are necessary for expression of male aggression in most strains of mice and perhaps humans as well (Loosen et al., 1994). Second, the emergence of aggression and violence typically occurs at puberty coinciding with increased secretion of sex steroid concentrations. Within the past three decades, a better appreciation of the broad endocrine correlates to aggressive behaviors has been obtained, but specifics have only recently emerged. In addition to precision in assaying hormones, additional insights into hormone–aggressive behavior interactions require precise behavioral analyses. Obtaining blood samples from individuals engaged in an aggressive encounter may not provide useful endocrine correlates without detailed behavioral analyses, or identification of the social status of

both participants. The term agonistic is used to describe the complete behavioral repertoire of both aggressive and submissive responses within the context of a social interaction involving a conflict of interest (Scott and Frederickson, 1951). However, submissive behaviors are not aggressive behaviors; consequently, hormonal mediation of the aggressive and the submissive components of an agonistic interaction likely differ (Leshner and Moyer, 1975). Hormones are closely associated with the regulation of aggressive behavior across species, but due to lack of space, this chapter focuses on mammals, primarily rodents and primates. This topic was similarly limited in the excellent chapter on this topic by Simon (2002) in the first edition of this volume. The interactions between hormones and aggression in non-mammalian species are detailed in **Chapter 23, Hormones, Brain, and Behavior in Reptiles**.

### 5.1.1 Categories of Aggression

Several categories of aggression are generally recognized (Table 1), and the different types of aggression have different neuroendocrine bases. The endocrine correlates of maternal aggression are vastly different from the endocrine correlates of territorial aggression. Maternal aggression, which serves to protect the offspring from intruders, appears to be mediated by hormonal changes associated with the production of offspring (Gammie et al., 2007). Specific relationships among blood concentrations of estrogens, progestins, prolactin, and corticotropin-releasing hormone (CRH) during the last days of pregnancy are correlated with the onset of maternal aggression.

Steroid hormones also underlie other types of aggressive behavior. Intermale aggression and territorial aggression, as well as sex- and rank-related aggression, all appear to be mediated by androgens

(Bouissou, 1983). These types of aggression are most commonly studied in the laboratory and are tested by the so-called resident–intruder paradigm (see below). Learned (or irritable) aggression is often studied in the form of restraint aggression, which results after an animal is held motionless. Another type of agonistic behavior commonly studied in the laboratory has been called fear-induced aggression, but this is more correctly termed defense. Notably, the physiological regulation control of aggression in these contrived situations is likely to differ from the physiological mechanisms underlying natural expressions of aggressive behavior. Most laboratory tests of hormone-aggressive behavioral interactions have been limited to isolation-induced and resident–intruder tests of males and maternal aggression of females.

To understand the mechanisms that underlie aggression, more precision is needed in reporting the antecedents and consequences of different types of aggression (Miczek et al., 2002). Thus, from an ethological perspective, aggression is used for obtaining or defending food or mates from competitors; from a psychiatric perspective, aggression is thought to be motivated by hypothetical constructs, such as anger, irritation, frustration, fear, and, in some cases, pleasure (Blair et al., 2006). Two subtypes of human aggression have been proposed: (1) the controlled–instrumental subtype and (2) the reactive–impulsive subtype (Vitiello and Stoff, 1997). Reactive aggression is considered to be impulsive (i.e., it is typically associated with anger), whereas instrumental aggression is considered to be purposeful and goal-oriented. Instigation of a physical fight with a stranger who accidentally bumps into you is an example of reactive aggression. This subtype of aggression can result in sudden, heightened, enduring, or inappropriate aggressive responses, and probably accounts for most societal problems that are associated with aggression (Blair et al., 2006). Reactive aggression is usually associated with impulse control and low serotonergic signaling (Krakowski, 2003; Mehlman et al., 1994). In contrast, high-profile incidents (e.g., mass killings, genocides, or assassinations) likely reflect instrumental mechanisms of aggression. Attacking or otherwise bullying your neighbors to intimidate them is an example of instrumental aggression. The controlled–instrumental subtype of aggression is thought to be regulated by higher cortical systems and is less dependent on the hypothalamic and limbic systems that are known to mediate impulsive aggression (Viding et al., 2007), and see below), and is likely to be less dependent on hormones than other types of aggression.

**Table 1** Types of aggression

Type of aggression	References
Antipredator aggression	Wilson (1975)
Defensive aggression (Fear-induced)	Moyer (1971)
Predatory aggression	Wilson (1975), Moyer (1971)
Dominance aggression (Intermale aggression)	Wilson (1975) Moyer (1971)
Maternal aggression	Moyer (1971)
Sex-related aggression	Wilson (1975), Moyer (1971)
Territorial aggression	Wilson (1975), Moyer (1971)
Irritable aggression	Moyer (1971)

Mental disorders, such as intermittent explosive disorder and post-traumatic 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 examples show the importance of considering the broader behavioral context when attempting to study the mechanistic bases of aggression. The development of animal models that mimic specific aggressive disorders should lead to additional insights into the mechanisms that underlie aggression (Haller and Kruk, 2006; Miczek et al., 2007a,b; Nelson and Trainor, 2007; Sluyter et al., 2003).

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? We will examine questions 2–4 in the following – because of space limitations, the external stimuli that elicit aggressive behavior will not be considered in depth. We will first 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.

## 5.2 Animal Models and Tests of Aggression

Is murine aggression a good model for human violence? Although mice and humans have >90% of their genes in common, and share some neuroanatomical similarities, the aggression observed in mice is rarely directly comparable, either in form, muscular output, or social consequences, to the violence displayed by humans (Sluyter et al., 2003). For example, male mice rarely focus their aggression toward females, whereas among humans, women are common targets of male violence (Crowell and Burgess, 1996). An important issue is as to what

extent underlying molecular mechanisms are similar between humans and mice. Choosing the appropriate animal model is critical to understanding the mechanisms underlying human violence.

Mice have become the most common animal model in the study of hormone–aggressive behavior interactions; however, most strains of laboratory mice (*Mus musculus*) have been bred to be docile. Consequently, mice must often be put into artificial situations that promote aggression, including individual housing. Several models of aggression focus on the offensive components of agonistic interactions in mice. Offensive behavior in this context is characterized by initiation on the part of the aggressive animal that often leads to damage to the opponents (Krsiak, 1974). It follows a defined temporal course, occurring in episodic fashion with epochs of intense, aggressive behavior alternating with relative quiescence (Miczek, 1983).

In male mice, isolation for several weeks induces an extensive repertoire of natural agonistic behaviors (Miczek and Krsiak, 1979). These singly housed mice are allowed to interact with nonaggressive group-housed male mice in an unfamiliar or neutral arena (isolation-induced aggression paradigm) or in their home cage (resident–intruder paradigm). During these confrontations, the attacker engages in pursuit, sideways threat, attack bites, and tail rattles, in addition to several nonagonistic activities, such as grooming, rearing, and locomotor activities (Nelson and Chiavegatto, 2000). 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. Because isolated mice (test animals) display more attacks as a resident (territorial aggression), which permits detection of both increases and decreases in aggression among individuals, the resident–intruder is the most extensive aggression test used in studies of hormone–behavior interactions among mice (Nelson and Chiavegatto, 2000). One important problem in conspecific confrontation is control of the stimulus animal, that is, the variation in the behavior of the nontest intruder. Because aggressive behavior of the resident is a function of interactions with the opponent (e.g., changes in social investigation), previous experiences of the intruder can confound the results. Thus, a previously defeated or naive 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.

In female mice, aggressive behavior is generally observed only when parturient females are approached by strange intruders during the first part of the lactating period (but see [Davis and Marler \(2004\)](#)). This so-called maternal aggression wanes as the young approach weaning ([Gammie et al., 2007](#)). Maternal aggression in females 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.

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](#)). After aggressive encounters have been experienced, however, aggressive behavior declines, but endures long after the surgery (e.g., [Christie and Barfield, 1979](#); [DeBold and Miczek, 1981, 1984](#)). Rather than having an obligatory role in the regulation of aggression among fish, reptiles, and birds, androgens appear to exert a modulatory effect on mammalian aggressive behavior ([Johnson and Whalen, 1988](#); [Miczek and Fish, 2006](#)).

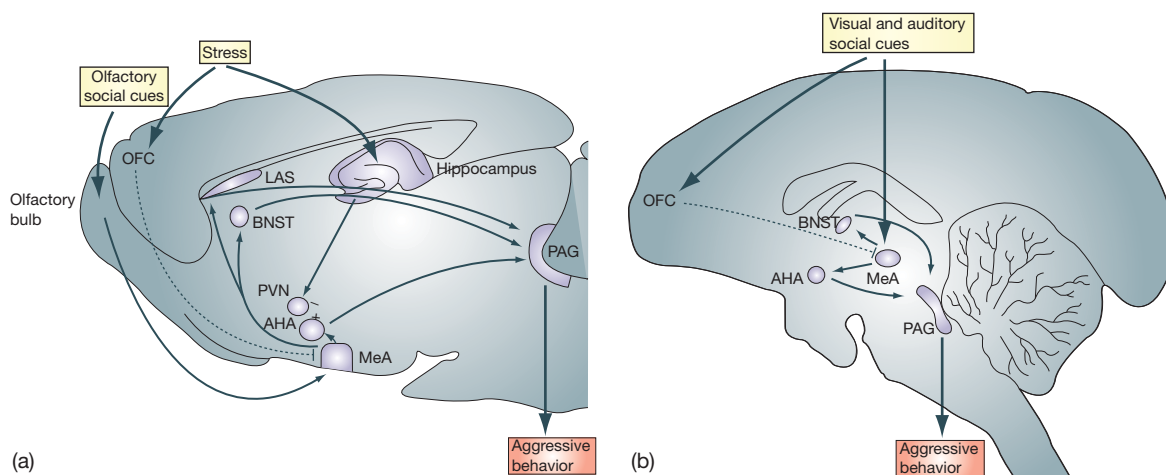
### 5.3 Brain Regions Contributing to Aggression

A complicating factor in studying neural circuits that affect 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 ([Choi et al., 2005](#); [Kollack-Walker and Newman, 1995](#)). Although there are 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 plays 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 ([Crews, 2003](#); [Goodson, 2005](#); [Gregg and Siegel, 2001](#)). Aggression is a primitive, 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.

#### 5.3.1 Studies in Rodents and Cats

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 (AH), ventral medial hypothalamus (VMH), and the periaqueductal gray region (PAG) ([Delville et al., 2000](#); [Wood and Newman, 1995](#)) ([Figure 1\(a\)](#)). This pathway is not linear, as there are many interconnections among these nuclei. 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 is thought to be more important in offensive contexts ([Swanson, 2000](#)). The components of this network have been identified mainly through lesion studies and investigations of immediate early gene expression. In general, lesions of the LAS, BNST, AH, and MeA reduce aggression between males ([Annen and Fujita, 1985](#); [Kruk, 1991](#); [Miczek et al., 1974](#)) ([Figure 1\(a\)](#)). Lesions of the orbitofrontal cortex (OFC) increase aggression in male rats ([de Bruin et al., 1983](#)), indicating that higher cortical networks have inhibitory effects on the social behavior network. Electrical stimulation of the AH increases male aggression ([Kruk](#)



**Figure 1** Neuroanatomical pathways of aggression in rodents and nonhuman primates. (a) In rodents, 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 behaviours. Stress can inhibit aggression via inhibitory inputs from the orbitofrontal cortex (OFC), the hippocampus, and the paraventricular nucleus (PVN). (b) In nonhuman primates, 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.

et al., 1984), whereas microinjection of a vasopressin antagonist (a neuropeptide known to affect aggression) into the AH decreases male aggression in hamsters (Ferris and Potegal, 1988). Investigation of immediate early gene expression has identified several nuclei that are activated by fighting. Immunostaining for the immediate early gene product *c-fos* is increased in the LAS, BNST, AH, and MeA after resident–intruder aggression tests (Delville et al., 2000; Kollack-Walker and Newman, 1995) and also following other aggressive events, such as maternal aggression (Gammie et al., 2007; Hasen and Gammie, 2005) and female–female aggression (Davis and Marler, 2004).

Similar circuitry has been identified in domestic cats (Gregg and Siegel, 2001). Electrical stimulation of the medial hypothalamus (including the VMH and mPOA) (Brutus et al., 1986), mediobasal amygdala (Shaikh et al., 1994), or PAG (Shaikh et al., 1993) promotes species-specific threat behaviors, including growling, hissing, and piloerection. Following aggressive behaviors, more *c-fos*-positive cells are observed in the medial hypothalamus (Bhatt et al., 2003), including the mPOA. This is in contrast to most rodent studies on intrasexual aggression (male–male or female–female), which usually report no increase in *c-fos*-positive cells in the mPOA. This difference could be due to either

species differences or context-specific stimuli related to how behavioral tests are conducted.

### 5.3.2 Nonhuman Primates and Humans

As in rodents, the hypothalamus seems to play a key role in regulating aggression in nonhuman primates (Figure 1(b)). Electrical stimulation of the ventromedial hypothalamus increases vocal threats and piloerection in male marmosets, *Callitrix jacchus* (Lipp and Hunsperger, 1978). Similarly, lesions of the AH and POA reduce vocal threats toward an intruder in male *C. jacchus* (Dixon and Lloyd, 1988). In rhesus monkeys (*Macaca mulatta*), electrical stimulation of the AH, BNST, or POA increases the frequency of aggressive vocalizations (Robinson, 1967), and increases aggression toward subordinate males (Alexander and Perachio, 1973).

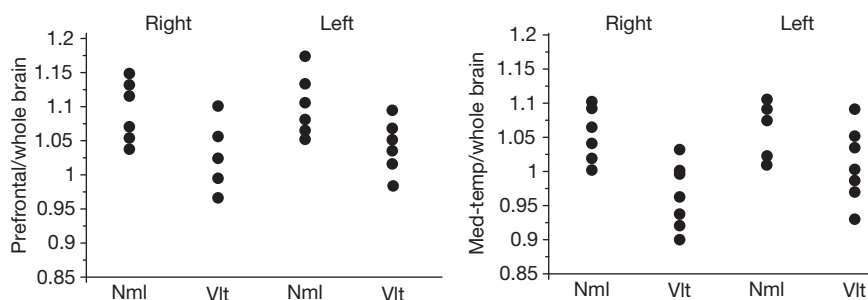
More recent studies have focused on the amygdala and OFC. Lesions of the amygdala either increase (Machado and Bachevalier, 2006) or decrease intermale aggression (Emery et al., 2001) in rhesus monkeys. One explanation for these conflicting results is that studies that reported increased aggression reintroduced 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 recent creative study used positron emission tomographic (PET) 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 magnetic resonance imaging (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; Soderstrom et al., 2000; Soloff et al., 2003; Volkow et al., 1995) (Figure 2). 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 (Anderson et al., 1999; Grafman et al., 1996). 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



**Figure 2** 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 (Vit). Reproduced from Volkow ND, Tancredi LR, Grant C. et al. (1995) Brain glucose metabolism in violent Psychiatry patients: A preliminary study. *Psychiatry Research* 61: 243–253, with permission from Elsevier.

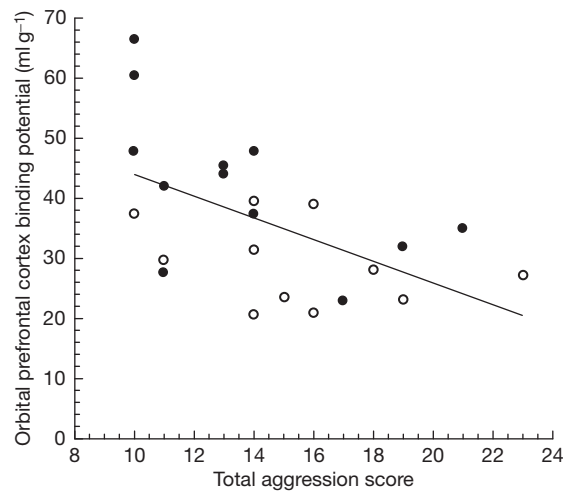
studies were usually crude and failed to account for the complexities of human behavior (Blair, 2004; Cherek et al., 2006; Scarpa and Raine, 2006; Trainor et al., 2006b). Additionally, electrolytic lesions damage fibers of passage as well as the target nuclei, and damage to the hypothalamus and amygdala affects general arousal (Tonkonogy and Geller, 1992), not just aggression. Although an experimental approach is desirable to infer cause and effect, a more integrative and ethical approach is required in studies of humans.

Several recent studies have taken an integrative approach to studying the neurobiological circuits that influence aggression. Previous studies reported reduced activation of the prefrontal cortex (PFC) 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 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, PET imaging studies using a selective serotonin receptor type 1A (5-HT<sub>1A</sub>) antagonist showed that scores on the LHA test were negatively correlated with 5HT<sub>1A</sub> binding in the amygdala and PFC (Parsey et al., 2002) (Figure 3). Intranasal administration of the neuropeptide hormone oxytocin to human participants reduced activation of the amygdala in response to fear-inducing pictures (e.g., sharks and snakes) (Kirsch et al., 2005). Studies in animals indicate that oxytocin can reduce aggression (DeVries et al., 1997; Winslow et al., 2000; Winslow and Insel, 1991) and that oxytocin receptors are abundant in the amygdala (Insel, 1992). Thus, oxytocin might reduce human aggressive responses in some contexts, although this hypothesis needs to be tested directly. These studies indicate that a combined approach with targeted biochemical manipulations, a realistic social context, and sophisticated measurements can allow investigators to test hypotheses that have been developed in animal models, ethically in humans.

## 5.4 Development of Aggression

### 5.4.1 Rough-and-Tumble Play as an Antecedent to Aggressive Behavior

Juveniles of most species engage in agonistic behaviors that at least superficially resemble adult



**Figure 3** Serotonin (5-HT) binding potential shows an inverse correlation 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. Reproduced from Parsey RV, Oquendo MA, Simpson NR, et al. (2002) Effects of sex, age, and aggressive traits in men on brain serotonin 5-HT<sub>1A</sub> receptor binding potential measured by PET using [C-11]WAY-100635. *Brain Research* 954: 173–182, with permission from Elsevier.

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 Pellis (1988, 1997, 1998) contend that play fighting and adult aggression are distinct behaviors, and that play fighting is not practice for adult fighting skills. 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 hindfeet remain on the ground (Pellis, 2002). Furthermore, infant (preweaning) rats display adult-like 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. Finally, 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 the cortex are associated with submissive behavior during adult aggression and negative affective states (Knutson et al., 2002; Panksepp et al., 2004).

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 (Cervantes et al., 2007; Delville et al., 2003; 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/subordinant status. Furthermore, because the SSRI 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 adult-like 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.

### 5.4.2 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 (non-human 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 Pellis (2002) and Wallen (1996)). In addition, human females with congenital adrenal hyperplasia (CAH), 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 receptors (ARs) and estrogen receptors (ERs) in the nervous system. The AR 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 ER activation also contributes to the masculinization of play behavior. Two of these experiments investigated play fighting in *tfn* rats, in which a mutation in the AR gene renders the receptor protein nonfunctional and the rats androgen-insensitive. Therefore, effects of testosterone, which is synthesized and secreted by *tfn* rats, are presumably due to ER activation after aromatization of testosterone to estradiol. The two investigations of play fighting in *tfn* rats are somewhat contradictory. One of them reports similar levels of play fighting in *tfn* and wild-type (WT) male rats, suggesting that ER-mediated mechanisms are sufficient to masculinize the behavior (Field et al., 2006). The other one reports that levels of play fighting are less in *tfn* than in WT males, supporting a role for AR-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.

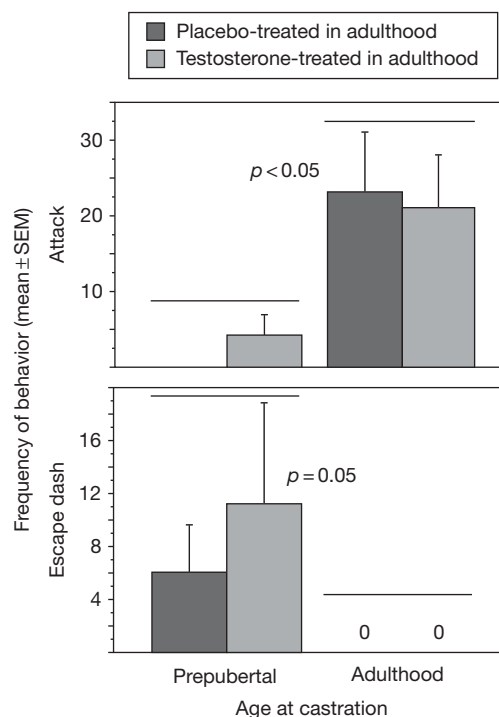
Interestingly, ER-mediated masculinization of play behavior may involve ligand-independent activation of the receptor. Administration of a dopamine (DA) D1 receptor agonist to neonatal female rats masculinizes their play-fighting behavior, and this effect can be blocked by prior treatment with the ER antagonist tamoxifen (Olesen et al., 2005). One central site of action of hormone-mediated masculinization of play fighting in rodents is 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). Overall, it appears that sexual differentiation of play fighting involves multiple hormones and multiple mechanisms of hormone receptor activation.

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 recent study found that girls with CAH are not only rated as more aggressive than unaffected girls, but are also 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 are also 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).

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

Another period of hormone-dependent organization of aggressive behavior occurs during puberty, when testicular hormone concentrations are once again elevated in males and when ovarian hormone cycles commence in females. 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. 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). 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 4). 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



**Figure 4** 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 KM and Sisk CL (2006) Pubertal hormones, the adolescent brain, and the maturation of social behaviors: Lessons from the Syrian hamster. *Molecular and Cellular Endocrinology* 254–255: 120–126, with permission from Elsevier.

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 postnatal day 1.

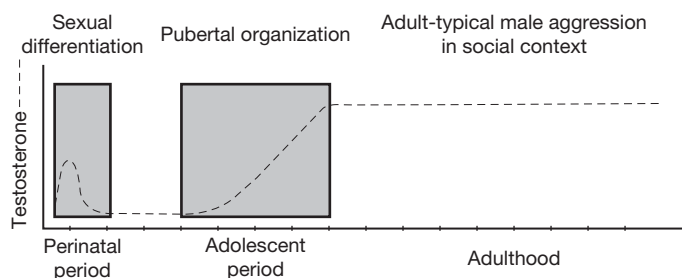
Overall, sexual differentiation of play fighting and adult aggression is a two-stage process involving gonadal hormone action in the nervous system during perinatal and pubertal periods of development. Perinatally, testicular hormones, via both androgenic and estrogenic action, drive the initial masculinization 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 5).

#### 5.4.4 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 tempting to conclude that pubertal hormones activate the behavior in particular social contexts. Indeed, as detailed in Section 5.5, 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 is clearly not under gonadal hormone control, because its occurrence is highest during the prepubertal and juvenile periods of life, when hormone levels are at their nadir. 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 AR- and ER-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 WT 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 ARs 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



**Figure 5** Development of male-typical aggressive behavior. The transient rise in testosterone during perinatal development is responsible for initial masculinization and defeminization of neural circuits that mediate aggressive behavior. These circuits are further organized during the pubertal rise in testosterone. These two stages of hormone-dependent organization program expression of male-typical aggressive behavior in specific social contexts in adulthood. Reproduced from Schulz KM and Sisk CL (2006) Pubertal hormones, the adolescent brain, and the maturation of social behaviors: Lessons from the Syrian hamster. *Molecular and Cellular Endocrinology* 254–255: 120–126, with permission from Elsevier.

toward rear) in hamsters appears to be due to increasing corticosteroid concentrations during puberty (Wommack and Delville, 2007).

#### 5.4.5 Experiential Contributions to the Development of Aggressive Behavior

Whether play fighting is a true precursor of adult aggression or not, the amount of juvenile play-fighting experience influences the expression of agonistic behaviors in adulthood. For example, male rats that are singly housed from 3–5 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 3–7 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 Section 5.4.6) (Huhman et al., 2003). Subjugation of hamsters after mid-puberty leads to an adult-typical response to subjugation; that is, 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.

#### 5.4.6 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 hypothalamic–pituitary–adrenal (HPA)-axis activity, such as increased plasma adrenocorticotrophic hormone (ACTH),  $\beta$ -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 re-exposure 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 are 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).

### 5.4.7 Aggression in Aged Individuals

Somewhat unexpectedly, at the other end of the lifespan, elevated 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 (Trainor et al., 2006b). For example, postmenopausal women using hormone replacement therapy (HRT) scored lower on hostility scales than women who did not use HRT (Olson et al., 2004; Steffen et al., 1999). These reports suggest that 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 first attack suggesting that the plaques and tangles associated with dementia may contribute to aggression (Minkeviciene et al., 2004).

## 5.5 Neurotransmitters, Hormones, and Aggression

### 5.5.1 Serotonin

Several classical neurotransmitters have been linked to aggression (Table 2), but data on serotonin (5-HT) are most compelling. Activation of the 5-HT system generally dampens aggression in animals and violent behavior in humans. Impulsivity and high aggressiveness are correlated with low cerebrospinal fluid concentrations of the 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 Merschedorf (2000)). Pharmacological strategies of increasing 5-HT levels,

such as the use of 5-HT precursors, SSRIs, as well as 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> receptor agonists are able to reduce aggressive behavior in rodents (reviewed in Manuck et al. (2006)).

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<sub>1B</sub> receptor is expressed in a variety of brain regions, including the basal ganglia, PAG, 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<sub>1B</sub> receptor gene (5-HT<sub>1B</sub><sup>-/-</sup>) are more aggressive than WT mice (Saudou et al., 1994). Lactating female 5-HT<sub>1B</sub><sup>-/-</sup> mice also attack unfamiliar male mice more rapidly and violently than WT mice (Ramboz et al., 1996). Notably, administration of the nonselective 5-HT<sub>1B</sub> agonist eltoprazine (one of the so-called serenics) significantly reduces aggressive behavior in both 5-HT<sub>1B</sub> knockout (KO) mice and WT mice, presumably by affecting 5-HT<sub>1A</sub> receptors (Ramboz et al., 1996). Although the 5-HT<sub>1B</sub> receptor contributes to aggression, these results suggest that the 5-HT<sub>1B</sub> receptor subtype is not the sole 5-HT receptor modulating aggressive behavior. Specifically, 5-HT<sub>1A</sub> receptor activation, which is also induced by eltoprazine, can also influence aggressive behaviors. Although both 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> receptors control the tone of the 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.

Androgens, either acting directly or via estrogenic metabolites, tend to facilitate aggression, whereas 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 (Cologer-Clifford et al., 1999; Simon et al., 1998; Sumner and Fink, 1998). Either testosterone or estradiol elevates 5-HT<sub>2A</sub> receptor mRNA expression and binding-site densities in male rat brains (Ferrari et al., 1999). Importantly, both androgens and estrogens modulate 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> 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.

**Table 2** Molecules that affect aggression

<i>Neurotransmitters and neuropeptides</i>	<i>Effects on aggression</i>	<i>References</i>
<i>Serotonin (5-HT)</i>		
Increase in 5-HT levels and decrease 5-HT <sub>1A</sub> agonists in rodents		Olivier et al. (1995), Miczek et al. (1998), Fish et al. (1999)
Lower 5-HT metabolite reduced 5-HT levels or turnover	Increase	Leschi and Merschdorf (2000), Lee and Coccaro (2001)
5-HT <sub>1B</sub> <sup>-/-</sup> male mice	Increase	Saudou et al. (1994)
5-HT <sub>1B</sub> <sup>-/-</sup> female mice	Increase	Ramboz et al. (1996)
<i>Histamine (HA)</i>		
HA intracerebral injection	Increase	Nath et al. (1982)
Decrease in HA levels	Decrease	Onodera et al. (1993)
H <sub>1</sub> -receptor blockers	Decrease	Noguchi et al. (1992)
H <sub>1</sub> <sup>-/-</sup> mice	Decrease	Yanai et al. (1998)
<i>Norepinephrine</i>		
β-Adrenoceptor blocker	Decrease	Haller et al. (1998)
α <sub>2</sub> -Adrenoceptor agonist	Increase	Haller et al. (1998)
α <sub>2</sub> -Adrenoceptor antagonist	Decrease/ increase	Haller et al. (1998)
α <sub>2C</sub> <sup>-/-</sup> Mice	Increase	Sallinen et al. (1998)
α <sub>2C</sub> Overexpressed mice	Decrease	Sallinen et al. (1998)
β-Hydroxylase knockout	Decrease	Marino et al. (2005)
<i>Dopamine</i>		
D <sub>2</sub> receptor agonists	Increase	Siegel et al. (1999)
D <sub>2L</sub> <sup>-/-</sup> mice	Decrease	Vukhac et al. (2001)
<i>Acetylcholine (ACh)</i>		
ACh muscarinic receptor agonists	Increase	Siegel et al. (1999)
Genetically developed cholinergic supersensitivity	Increase	Pucilowski et al. (1990–1991)
<i>Gamma-aminobutyric acid (GABA)</i>		
GABA <sub>A</sub> receptor agonist	Decrease	Siegel et al. (1999)
GABA receptor antagonists	Increase	Siegel et al. (1999)
GAD65 <sup>-/-</sup> and GAD65 <sup>+/-</sup> mice	Decrease	Stork et al. (2000)
<i>Glutamate</i>		
Glutamate agonists	Increase	Siegel et al. (1999)
<i>Adenosine</i>		
A <sub>1</sub> -receptor agonist	Decrease	Navarro et al. (2000)
A <sub>2A</sub> <sup>-/-</sup> mice	Increase	Ledent et al. (1997)
<i>Substance P (SP)</i>		
SP administration in mice	Decrease	Chapman et al. (1995)
NK-1 receptor antagonist in rats	Increase	Ehret et al. (1989)
NK-1 receptor antagonist in cats	Decrease	Navarro et al. (2000)
NK-1 <sup>-/-</sup> mice	Decrease	Heximer et al. (1997)
<i>Opioid Peptides</i>		
Different opioid receptor agonists	Decrease	Benton (1985)
Morphine	Decrease	Haney and Miczek (1989), Kantak and Miczek (1986)
Reduced met-enkephalin content	Increase	Diaz and Asai (1990)
Enkephalin-deficient mice (enk <sup>-/-</sup> )	Increase	Konig et al. (1996)
<i>Cholecystokinin (CCK)</i>		
CCK <sub>B</sub> agonist	Increase	Luo et al. (1998)
CCK <sub>B</sub> antagonist	Decrease	Luo et al. (1998)

Continued

**Table 2** Continued

<i>Neurotransmitters and neuropeptides</i>	<i>Effects on aggression</i>	<i>References</i>
<i>Arginine vasopressin (AVP)</i>		
AVP microinjection	Increase	Ferris et al. (1997)
Increased AVP levels	Increase	Coccaro et al. (1998)
Increased AVP neuronal activity	Increase	Deville et al. (2000)
AVP receptor antagonist	Decrease	Ferris and Potegal (1988)
<i>Oxytocin (OT)</i>		
OT <sup>-/-</sup> mice	Decrease/ increase	DeVries et al. (1997), Winslow et al. (2000)
<i>Nitric oxide (NO)</i>		
Inhibition of neuronal NOS in male mice	Increase	Demas et al. (1997)
Neuronal NOS <sup>-/-</sup> male mice	Increase	Chiavegatto et al. (2001), Nelson et al. (1995)
Inhibition of neuronal NOS in female prairie voles	Decrease	Gammie et al. (2000)
Neuronal NOS <sup>-/-</sup> female mice	Decrease	Gammie et al. (1999)
Endothelial NOS <sup>-/-</sup> male mice	Decrease	Demas et al. (1999a)
Endothelial NOS <sup>-/-</sup> female mice	No difference	Gammie et al. (2000)
<i>Steroid hormones</i>		
<i>Androgens</i>		
Androgens	Increase	Simon et al. (1998)
Androgen receptor mutant mice (spontaneous)	Decrease	Maxson (2000)
<i>Estrogens</i>		
Aromatase P450 <sup>-/-</sup> mice	Decrease	Toda et al. (2001)
Estrogen receptor ( $\alpha$ -isoform) <sup>-/-</sup> male mice	Decrease	Ogawa et al. (1997), Scordalakes and Rissman (2003)
Estrogen receptor ( $\beta$ -isoform) <sup>-/-</sup> female mice	Increase	Ogawa et al. (1998)
Estrogen receptor ( $\beta$ -isoform) <sup>-/-</sup> male mice	Normal or increase	Ogawa et al. (1999), Nomura et al. (2002), Nomura et al. (2006)
Estrogen receptor ( $\alpha\beta$ -isoform) <sup>-/-</sup> male mice	Decrease	Ogawa et al. (2000)
Glucocorticoids	Increase	McEwen (2000)
Adrenalectomy	Increase	Haller et al. (2001)
<i>Metabolic enzymes</i>		
<i>Monoamine oxidase A (MAOA)</i>		
MAOA inhibition in rodents	Decrease	Florvall et al. (1978), Datla and Bhattacharya (1990)
MAOA <sup>-/-</sup> mice	Increase	Cases et al. (1995)
MAOA deficiency (point mutation) in humans	Increase	Brunner et al. (1998)
<i>Catechol-O-methyltransferase (COMT)</i>		
COMT <sup>-/-</sup> mice	No difference	Gogos et al. (1998)
COMT <sup>+/-</sup> mice	Increase	Gogos et al. (1998)
<i>Neutral endopeptidase (NEP)</i>		
NEP <sup>-/-</sup> mice	Increase	Fischer et al. (2000)
<i>Cytokines/growth factors (neurotrophins)</i>		
<i>Interleukin-1 <math>\beta</math> (IL-1 <math>\beta</math>)</i>		
IL-1 $\beta$ administration	Decrease	Cirulli et al. (1998)
<i>Interleukin-6 (IL-6)</i>		
IL-6 <sup>-/-</sup> mice	Increase	Alleva et al. (1998)
IL-6 overexpression in mice	Decrease	Alleva et al. (1998)
<i>Transforming growth factor <math>\alpha</math> (TGF<math>\alpha</math>)</i>		
TGF $\alpha$ overexpression in mice	Increase	Hilakivi-Clarke et al. (1992)
<i>Brain-derived neurotrophic factor (BDNF)</i>		
BDNF <sup>+/-</sup> mice	Increase	Lyons et al. (1999)

Continued

**Table 2** Continued

Neurotransmitters and neuropeptides	Effects on aggression	References
<i>Signaling proteins</i>		
$\alpha$ -Ca <sup>2+</sup> -Calmodulin-dependent kinase II ( $\alpha$ -CaMKII)		
$\alpha$ -CaMKII <sup>-/-</sup> mice	Decrease	Chen et al. (1994)
$\alpha$ -CaMKII <sup>+/-</sup> mice	Increase	Chen et al. (1994)
<i>Regulator of G-protein signaling-2 (RGS2)</i>		
Rgs2 <sup>-/-</sup> mice	Decrease	Oliveira-Dos Santos et al. (2000)
<i>Breakpoint cluster region (BCR)</i>		
Bcr <sup>-/-</sup> mice	Increase	Voncken et al. (1998)
<i>VGF polypeptide</i>		
VGF <sup>-/-</sup> mice	Decrease	Hahm et al. (1999)

Reproduced from Nelson RJ and Trainor BC (2007) Neural mechanisms of aggression. *Nature Reviews Neuroscience* 8: 536–546, with permission from the Nature Publishing Group.

### 5.5.2 Arginine Vasopressin

Arginine vasopressin (AVP) is another hormone that plays a critical role in aggression and other social behaviors (Ferris, 2006; Goodson and Bass, 2001). The effects of AVP on aggression, centered in the AH, appear to be mediated by 5-HT receptor subtypes, 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, and AVP V<sub>1A</sub> receptors (Albers et al., 2002). Microinjections of AVP into the AH of hamsters in combination with 5-HT<sub>1A</sub> or 5-HT<sub>1B</sub> receptor agonists revealed that only the 5-HT<sub>1A</sub> 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<sub>1A</sub> receptors (Ferris, 2006).

### 5.5.3 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 the oxidative deamination of 5-HT, norepinephrine, and DA with high affinity (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 (Buckholtz and Meyer-Lindenberg, 2008; Manuck et al., 2006). 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 the MAOA deficiency state, throughout life, likely accounts for the effects on aggression. Notably, the elevated aggression in humans and mice with MAOA gene disruption mostly affects males (Buckholtz and Meyer-Lindenberg, 2008; Manuck et al., 2006). MAOA activity is directly regulated by estrogen (Chakravorty and Halbreich, 1997). Testosterone or estradiol could influence aggression via several hormone response elements in the MAOA promoter (Ou et al., 2006).

### 5.5.4 Nitric Oxide

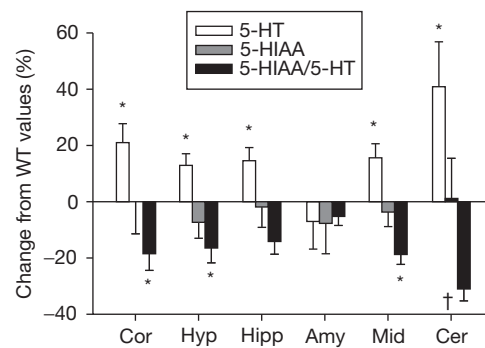
Nitric oxide (NO) was initially identified as an endogenous regulator of blood vessel tone, but is now recognized as a neurotransmitter in both the central and the peripheral nervous systems (Baranano and Snyder, 2001). NO has a rapid half-life *in vivo*, thus manipulation of NO has been accomplished indirectly by targeting its synthetic enzyme, nitric oxide synthase (NOS), that transforms arginine into NO and citrulline. Male mice with targeted deletion of the gene encoding the neuronal version of NOS (nNOS<sup>-/-</sup> or NOS1<sup>-/-</sup>) displayed 3–4 times more aggressive behaviors than WT mice in the intruder–resident test (Nelson et al., 1995). Nearly 90% of the aggressive encounters were initiated by the nNOS<sup>-/-</sup> animals. In all test situations, male nNOS<sup>-/-</sup> 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 KO 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 mice do not differ between WT and nNOS<sup>-/-</sup> mice either before or after aggressive interactions (Nelson et al., 1995). However, castrated nNOS<sup>-/-</sup> mice indicate that testosterone is necessary, if not sufficient, to maintain elevated aggression in these KO mice (Kriegsfeld et al., 1997). Androgen replacement therapy restored the elevated levels of aggression to precastration levels in both nNOS<sup>-/-</sup> and WT mice.

5-HT function was hypothesized to be disrupted in the aggressive nNOS<sup>-/-</sup> mice because of the inverse relation of 5-HT system activity and aggression. 5-HT metabolism, analyzed by the ratio of the metabolite 5-HIAA and 5-HT levels by high-performance liquid chromatography (HPLC), was significantly 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 6). The disturbed neurochemical profile appears specific to the 5-HT system, because norepinephrine, DA, and metabolites were generally unaffected. As noted, MAO has been implicated in aggression; however, the relatively normal norepinephrine and DA values suggest that it is unlikely that alterations in MAO account for the 5-HT abnormalities in the nNOS KO 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 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). Castration decreases the number of nNOS-positive neurons in male rats



**Figure 6** 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<sup>-/-</sup> as compared to WT mice. Data are percent change in relation to WT mice  $\pm$  SEM; \* $p < 0.05$ . Reproduced from Chiavegatto S, Dawson VL, Mamounas LA, Koliatsos VE, Dawson TM, and Nelson RJ (2001) Brain serotonin dysfunction accounts for aggression in male mice lacking neuronal nitric oxide synthase. *Proceedings of the National Academy of Sciences of the United States of America* 98: 1277–1281.

(Du and Hull, 1999) and hamsters (Hadeishi and Wood, 1996). Other studies have indicated elevated hypothalamic nNOS mRNA of male rats after castration (Shi et al., 1998; Singh et al., 2000). Estradiol treatment seems to increase nNOS activity in the ventrolateral nucleus of guinea pigs (Warembourg et al., 1999) and in the PVN (Sanchez et al., 1998) and MPA (Okamura et al., 1994) of rats. These discrepancies in the effects of gonadal hormones on nNOS 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.

## 5.6 Endocrine Signals and Receptors Contribution to Aggression

### 5.6.1 Steroid Hormones

Steroid hormones have 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 5 $\alpha$ -dihydrotestosterone (DHT) and 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 an important impact on the behavioral effects of circulating hormones.

### 5.6.1.1 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. During the subsequent 150 years, similar 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 (Bales et al., 2006; Lincoln et al., 1972; Moore, 1986; Wingfield, 1984). Similarly, male aggressive behavior often increases at the time of puberty (Delville et al., 2005; Pellis et al., 1997; Wallen et al., 1991), 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), 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 (Ketterson and Nolan, 1992; Wingfield et al., 1987) and spiny lizards (*Sceloporus jarrovi*) (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, 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 either against lactating females or olfactory bulbectomized males (reviewed in Johnson and Whalen (1988)). Gonadally 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.

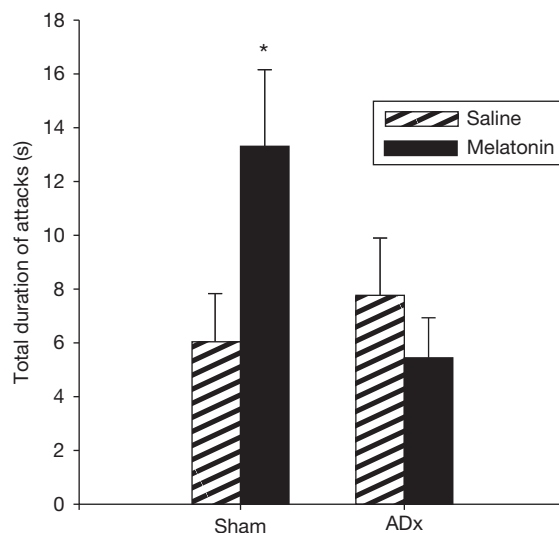
Although baseline testosterone concentrations regulate aggression in many species, recent studies have identified several species in which castration does not reduce male aggression (Caldwell et al., 1984; Demas et al., 1999; Trainor et al., 2006a; Trainor and Marler, 2001). Furthermore, dominance in 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 (Dixon, 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). 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 almost immediately. 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 (Chase et al., 1994; Kudryavtseva, 2000; Parmigiani and Brain, 1983), even when variables, such as intrinsic fighting ability, are controlled (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). Recent studies have demonstrated that injections of testosterone 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.

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; Soma, 2006; Young et al., 1996), raising the possibility that the brain may be producing androgens independently of the testes. Recent studies have begun to focus on the role of dehydroepiandrosterone (DHEA), which 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 7) 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. This mode of action may be critical to sustain aggression outside of the breeding season when testosterone concentrations are low. As suggested above, testosterone sometimes exerts behavioral effects indirectly through its conversion to estrogens.

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 salivary androgen concentrations and aggressiveness (Doering et al., 1975; Monti et al., 1977; Persky et al., 1977). However,



**Figure 7** Melatonin increases aggressiveness in adrenal-intact Siberian hamsters. Mean ( $\pm$ SEM) total duration of attacks (s) in hamsters that received bilateral adrenalectomies (ADx) or sham operations (Sham) and subsequently were treated with either melatonin or control (Saline) injections. \* $p < 0.05$ . Reproduced from Demas GE, Polacek KM, Durazzo A, and Jasnow AM (2004) Adrenal hormones mediate melatonin-induced increases in aggression in male Siberian hamsters (*Phodopus sungorus*). *Hormones and Behavior* 46: 582–591, with permission from Elsevier.

relationships between blood testosterone concentrations and behavior have been reported among aggressive, violent, and antisocial individuals, especially those incarcerated in prison (Ehrenkranz et al., 1974; Kreuz and Rose, 1972). Prison inmates with high circulating testosterone concentrations, usually defined as the top 5% or 10% of the normal distribution, had committed violent crimes (Dabbs et al., 1987, 1988; Ehrenkranz et al., 1974), 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 (e.g., 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 United States 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). However, given the correlation nature of these results, a role for environmental factors cannot be discounted.

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 (Dabbs and Hargrove, 1997; Dabbs et al., 1988; Persky et al., 1977). 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).

### 5.6.1.2 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 KO mice display low-aggression levels in resident-intruder tests (Matsumoto et al., 2003; Toda et al., 2001). In Swiss Webster (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).

Estrogens can bind to one of at least two ER subtypes,  $\alpha$  and  $\beta$ . Most of what is known about the effects of these receptors on aggression comes from a series of studies on KO mice. Male mice with targeted disruption of ER $\alpha$  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 ER $\alpha$  KO mice are more likely than WT mice to attack female intruders. In male CD-1 mice, levels of aggression directed toward other males are positively correlated with the number of ER $\alpha$ -immunopositive cells in the LAS, BNST, and AHA (Trainor et al., 2006a). The deletion of ER $\beta$  is generally associated with increased aggression (Nomura et al., 2006; Ogawa et al., 1999), 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 KO studies, the effects of ER $\alpha$  and ER $\beta$  could be organizational, activational, or both. Recent studies using ER-specific ligands in adult animals have suggested that the directional effects of these ER $\alpha$  and ER $\beta$  may occur primarily during development (see Section 5.7), although additional studies are needed to test this hypothesis.

### 5.6.1.3 Glucocorticoids

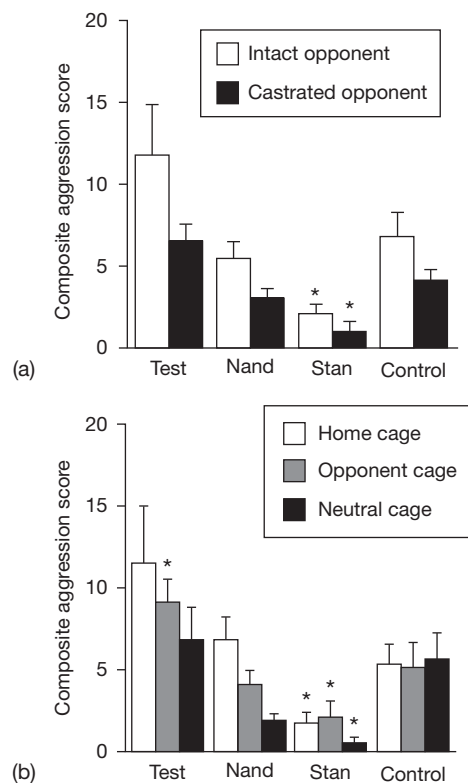
The effects of glucocorticoids on aggression are also variable, although the mechanistic basis for this is poorly understood. Generally, chronic elevations in glucocorticoid concentrations (usually associated with stress) inhibit aggressive behavior (Leshner et al., 1980; Maestripieri et al., 1991; Summers 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 5-HT (Meijer and de Kloet, 1998), and increase glutamate neurotransmission in the frontal cortex (Moghaddam, 2002). All of these physiological responses could contribute to reduced aggressive behavior. 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 non-genomic 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 increase in glucocorticoids are mediated by nongenomic responses of membrane receptors.

### 5.6.2 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., 2007). 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; Galligani et al., 1996; Pope and Katz, 1994). 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 8). 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



**Figure 8** 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 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 SF and McGinnis MY (2003) Effects of pubertal anabolic-androgenic steroid (AAS) administration on reproductive and aggressive behaviors in male rats. *Behavioral Neuroscience* 117: 904–911, with permission from American Psychological Association.

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 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, also known as stacking (Trenton and Currier, 2005). Studies in hamsters show that activation of 5HT<sub>1B</sub> receptors blocks the effects of androgenic cocktail (testosterone cypionate, nortestosterone, and DHT)

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 AVP immunoreactivity (Grimes et al., 2007) and baseline c-fos immunoreactivity (Ricci et al., 2007) in the AH, a nucleus 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 US report having used anabolic androgens (Johnston et al., 2005). 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 (Harrison et al., 2000; Melloni et al., 1997), and anabolic steroid-induced increases in aggression are more robust in adolescents 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.

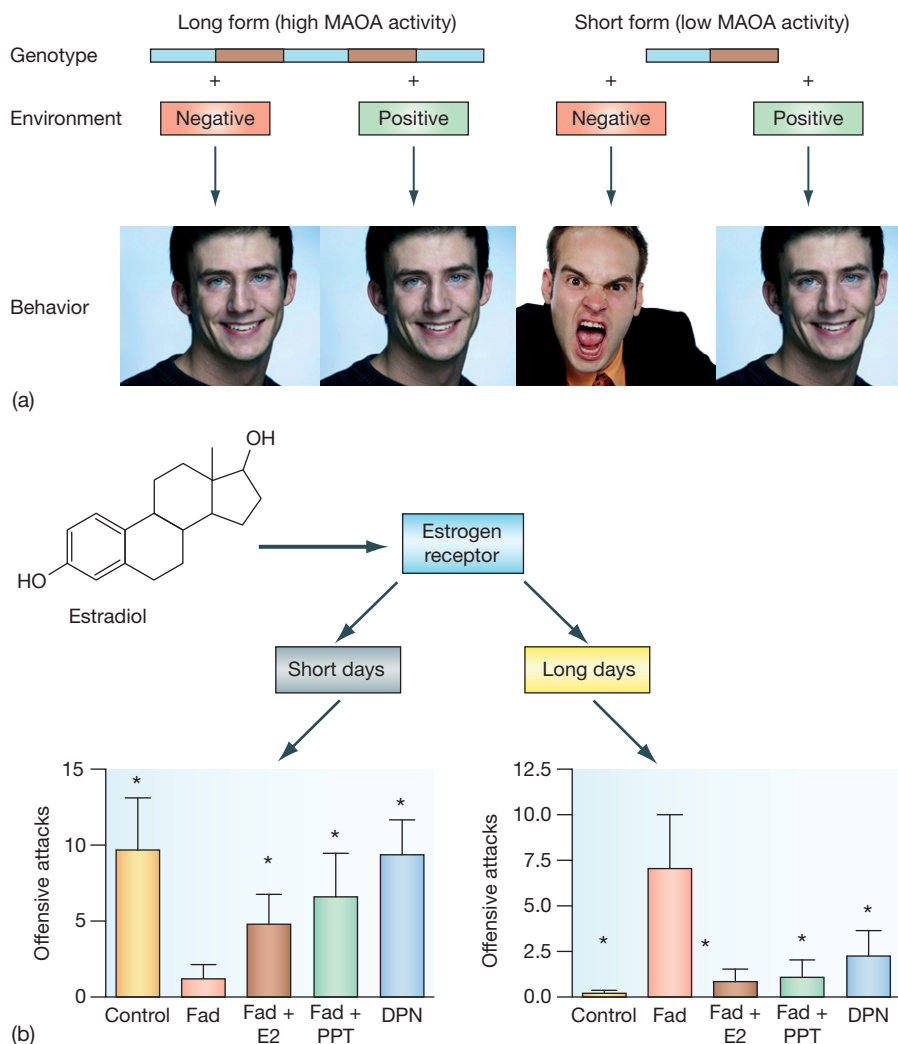
### 5.6.3 Reciprocal Effects of Aggression on Steroid Hormones

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 have lost a fight in paired aggressive encounters (Huhman and Jasnow, 2005; Lloyd, 1971). 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).

## 5.7 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, recent studies have demonstrated that several neurochemical pathways of aggression function differently depending on the environment.

The effects of the repeat length polymorphism in the human MAOA gene appear to interact with environmental influences. Caspi and colleagues (Caspi et al., 2003a) reported that the effect of child abuse on behavior was significantly stronger if the child carried alleles associated with low MAOA activity (Figure 9(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 association 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). A meta-analysis of these studies indicated that, on average, children with genotypes for low MAOA activity have elevated rates of antisocial



**Figure 9** Gene-environment interactions in humans and mice. (a) The interaction between the monoamine oxidase A (MAOA) genotype and the rearing environment affects aggressive behavior. 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. (b) Photoperiod determines the directional effects of estrogens on aggressive behavior in beach mice (*Peromyscus polionotus*). *P. 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 co-treatment 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)- $\alpha$  agonist) and DPN (diarylpropionitrile, an ER $\beta$  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). (a) Based on a paper by Caspi A, McClay J, Moffitt TE, et al. (2003a) Role of genotype in the cycle of violence in maltreated children. *Science* 297: 851–854. (b) Reproduced from Trainor BC, Lin S, Finy MS, Rowland MR, and Nelson RJ (2007a) Photoperiod reverses the effects of estrogens on male aggression via genomic and non-genomic pathways. *Proceedings of the National Academy of Sciences of the United States of America* 104: 9840–9845.

behavior when exposed to parental maltreatment (Kim-Cohen et al., 2006). Although further study is needed, these results indicate that certain genetic backgrounds might confer resistance to adverse

environmental conditions, which could partially explain why many abused children do not show increased antisocial behavior. Allelic variation in MAOA activity also interacts with early environment

in rhesus monkeys to influence the expression of aggressive behavior (Newman et al., 2005).

Although the effects of gene–environment interactions can also be seen in 5-HT-regulated behaviors, such as depression (Caspi et al., 2003b), there is less evidence that environmental factors interact with variability in the 5-HT transporter (5HTT) gene to influence aggression. The short allele of the 5HTT gene is associated with reduced expression of 5HTT in the brain and inefficient reuptake of 5HT from the synapse (Greenberg et al., 1999). The interaction between stress and 5HTT 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). Several studies have indicated that the short allele is associated with exaggerated responses to stress (Barr et al., 2004; Canli et al., 2006; Furmark et al., 2004).

In rodents, several studies have demonstrated that parental behaviors can influence the effects of gene on aggression. Males of the NZB strain are more aggressive than 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 *P. californicus* are more aggressive than male *P. 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).

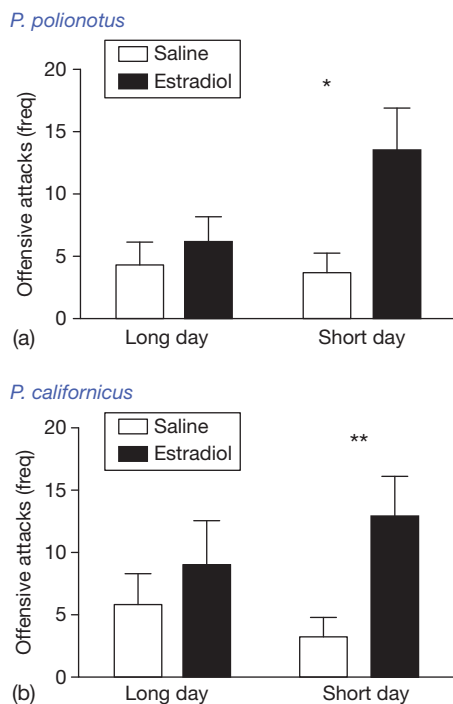
The context in which mice are tested can also have important effects on behavior. Male mice are usually more aggressive in resident–intruder tests (when intruders are introduced into a resident's home cage), compared to neutral tests (when two mice are introduced into a neutral arena). Patterns of aggression 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 in a resident–intruder test (Guillot et al., 1994), but is absent if mice are tested in a neutral arena (Roubertoux et al., 1999). 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 (*Stx*) 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 directional effects of estrogens on male aggressive behavior (Figure 9(b)). Similar to hamsters, three species of *Peromyscus* are more aggressive when exposed to short days than when exposed to long days (*P. maniculatus* and *P. polionotus* Trainor et al. (2007b); *P. californicus* Nelson and Trainor (2007)). 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 ER $\alpha$  agonist propylpyrazole-triol (PPT) and the ER $\beta$  agonist diarylpropionitrile (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

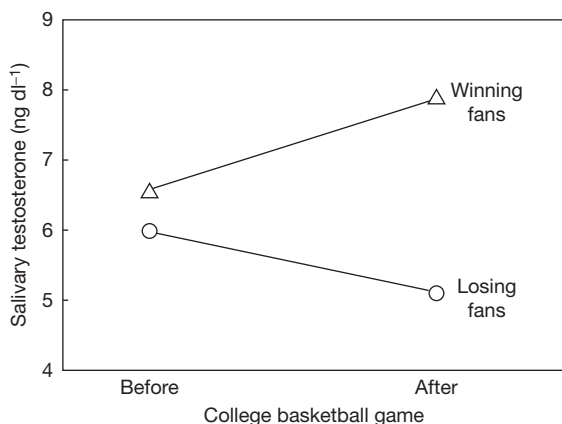
mice, suggesting estrogens might act via nongenomic pathways in mice exposed to short days. In *P. polionotus*, estradiol injections acted rapidly (15 min) to increase aggression in short-, but not long-day, mice suggesting that estradiol increases aggression via nongenomic action (Trainor et al., 2007a). This same result was also observed in *P. californicus* (Trainor et al., 2008) (Figure 10). These data suggest that the environment regulates the effects of steroid hormones in *Peromyscus* by determining the molecular pathways that are activated by steroid receptors. The effects of estrogen may also be age dependent. Aggressive behavior in ER $\beta$ KO mice is increased compared to WT litter-mates in younger male mice (12 weeks) whereas this effect is less pronounced in older males (>18 weeks old) (Nomura et al., 2002).

## 5.8 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. Recent studies have demonstrated that 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 11). 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



**Figure 10** The rapid effect of estradiol injection on aggression depends on photoperiod. Estradiol acts rapidly to increase aggression when male (a) *P. polionotus* or (b) *P. californicus* are housed in short days, but not long days. \* $p < 0.05$ , \*\* $p < 0.01$ . (a) Reproduced from Trainor BC, Lin S, Finy MS, Rowland MR, and Nelson RJ (2007a) Photoperiod reverses the effects of estrogens on male aggression via genomic and non-genomic pathways. *Proceedings of the National Academy of Sciences of the United States of America* 104: 9840–9845. (b) Reproduced from Trainor BC, Finy MS, and Nelson RJ (2008) Estradiol increases short-day aggression in a non-seasonally breeding rodent. *Hormones and Behavior* 53: 192–199, with permission from Elsevier.



**Figure 11** Basketball fans' testosterone levels before and after their team has won or lost. Reproduced from Bernhardt PC, Dabbs JM, and Fielden JA (1998) Testosterone changes during vicarious experiences of winning and losing among fans at sporting events. *Physiology and Behavior*. 65: 59–62, with permission from Elsevier.

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 (Soloff et al., 2003; Volkow et al., 1995). Biology-based approaches to examining 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.

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### Relevant Website

<http://www.nida.nih.gov> – Research Report Series: Anabolic Steroid Abuse, National Institute of Drug Abuse.

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