Social neuroendocrinology: Functional role of testosterone dynamics

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An Evolutionary Science of Human Behavior: An Interdisciplinary Approach

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A large body of evidence indicates that hormones modulate various physiological, morphological and behavioral processes critical to survival and reproduction (Ketterson & Nolan, 1992). Notably, changes in the social environment are known to alter hormonal concentrations over both the short-term (e.g., competitive interactions) and long-term (e.g., acquiring a long-term mate, becoming a father). In this chapter, we provide a basic overview of research examining the functional significance of acute short-term fluctuations in testosterone. We first provide a basic overview of the neuroendocrine system, describing different types of hormones and how they act to modulate physiology and behavior. Next, we review a growing body of literature demonstrating the critical role of the social environment in modulating testosterone concentrations. Finally, we discuss an emerging literature examining the role of acute fluctuations in testosterone in potentiating ongoing and/or future competitive, aggressive, risk-taking and mate-seeking behavior. In this chapter, we take a comparative approach drawing on both the human and non-human literature to provide a sense of the commonalities in the basic neuroendocrine mechanisms underlying complex social behavior.

HORMONE PRIMER

In 1849, Arnold Berthold performed the first formal experiment in behavioral neuroendocrinology. Berthold's experiments consisted of removing the testes of male roosters and observing how this manipulation influenced behavior. The results were fascinating: the roosters stopped crowing and did not develop secondary sex characteristics (e.g., large comb) and they also ceased engaging in sexual and aggressive

behavior – all classic behaviors expressed by male roosters. Berthold then re-implanted the testes into the body cavity of the roosters, and the male phenotypes returned. Since the testes did not form neural connections after being placed in the body cavity, Berthold concluded that the testes must produce and release a chemical substance into the bloodstream, influencing the male typical phenotype.

Today we know that the crucial chemical released by the testes is testosterone. We also know that there are numerous other hormones secreted by this and other endocrine glands which have profound effects on physiological and behavioral processes including; reproduction, growth and development, regulation of metabolism, aggression, pair-bonding, and parental behavior. The glands that make up the endocrine system include the pituitary gland, pancreas, thyroid gland, adrenal glands, pineal gland, placenta, ovaries and testes. Hormones are chemical messengers produced by endocrine glands and released into general circulation. By traveling through the bloodstream, hormones have the distinct ability to affect both nearby and distant targets. Historically it was understood that hormones worked primarily as long distance internal messengers and that their effects were quite delayed compared to neurostransmitters. However, a wealth of research in behavioral neuroendocrinology now indicates hormones can have rapid effects on both physiology and behavior (Michels & Hoppe, 2008) and are not only produced and secreted by endocrine glands but can also be manufactured de novo directly by the brain (Adkins-Regan, 2005).

Steroid Hormones

Steroids are perhaps some of the most well-known of the hormones. In the popular press, steroids are described mainly in the context of performance-enhancing drugs used by bodybuilders and professional athletes to gain a physical and psychological edge on their opponents. Although it is true that performance-enhancing drugs such as testosterone can have profound effects on muscle physiology (Bhasin et al., 1996) and status-seeking behavior (Eisenegger, Haushofer, & Fehr, 2011), it is just one of the many hormones that belong to a class of hormones called ‘steroids’. All steroid hormones are derived from cholesterol and share a common four ring structural composition. With variations to this standard structure come the many different types of steroids including androgens, estrogens, progestogens, and corticosteroids.

Steroid hormones are highly conserved across species and have two distinct characteristics that separate them from most other hormones. First, because steroids are lipophilic they are not readily soluble in blood and thus, a large fraction (>90%) of each particular steroid hormone is transported in the bloodstream via large protein carriers. Second, steroid hormones easily pass through cell membranes and interact with intra-cellular receptors. Upon entering the cell, steroid hormones bind to intracellular receptors creating a steroid-receptor complex. This steroid-receptor complex then binds to hormone response elements located in promoter regions of various steroid regulated genes whereby they alter gene transcription, and ultimately influence the production of peptides and proteins. In the central nervous system the protein products may include enzymes for steroid synthesis and metabolism, steroid/peptide/neurotransmitter receptors, enzymes for the production of neurotransmitters, ion channels, and proteins for building/repairing axons, dendrites and synapses (Adkins-Regan, 2005). In addition to their slow genomic mode of action (i.e., it may take several minutes to hours for steroid hormones to influence gene transcription and subsequent protein formation), steroid hormones may

influence physiological processes within seconds, suggesting that they may be acting via non-genomic, membrane-bound receptors (Michels & Hoppe, 2008). The rapid effects of steroid hormones through membrane-bound receptors and/or ion channels may also trigger downstream second messenger processes within the cell, which, in turn, may modulate gene transcription. Thus, steroid hormones have the potential to influence physiological and behavioral processes by acting through both slow- and/or fast acting biological mechanisms

Peptide Hormones

Peptide hormones are amino acid based molecules that are primarily stored in membrane bound secretory granules and are released into the bloodstream by exocytosis. In contrast to steroid hormones, the specific structure of peptides differs greatly among species. Also, peptides are readily soluble in blood, and thus, do not need to bind to protein carriers to travel within the bloodstream. Because peptides are free floating they tend to have a much shorter half-life compared to steroid hormones that are bound to carrier proteins. Peptides are polar molecules and do not have the ability to easily enter a cell membrane, and thus, instead of entering the cell directly, peptides bind to receptors found within the cell membrane. Once the peptide is bound to a receptor it initiates a cascade of responses that effect intracellular events. These cascades involve mechanisms such as modulation of G protein receptors and/or ion channels. In the case of G protein receptors, the peptide hormone binds to the receptor converting its configuration and kick starting a multi-step reaction that ultimately alters the functioning of the cell. Peptides have powerful effects on processes having critical importance for survival and reproduction. For example, oxytocin (OT), a peptide hormone secreted by the posterior pituitary gland, plays a key role in promoting uterine contractions during childbirth and milk letdown during breastfeeding. Inspired by research in animal models (Young & Wang, 2004), the past decade has seen an explosion of OT administration work examining its effects on a wide range of behaviors including trust, reciprocity, pair-bonding and aggression (Bartz, Zaki Bolger, & Ochsner, 2011: Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011).

Regulation of Hormones

The central nervous system and endocrine system interact in complex ways. The primary means by which these systems interact is through a communication system involving the hypothalamus and pituitary gland. The pituitary gland is capable of making and secreting up to nine different hormones that target tissues and other endocrine glands throughout the body. The interaction between the pituitary gland and the hypothalamus creates the perfect command station for the endocrine system and is often the beginning of a cascade of hormones acting on other hormones and target cells. The hypothalamus interacts with the pituitary gland in two distinct ways. The first involves the hypothalamus and anterior pituitary gland. These two structures are connected through a vascular system known as the hypophyseal portal system. The anterior pituitary gland is where many hormones are originally synthesized and secreted. These hormones include thyroid-stimulating hormone, luteinizing hormone, follicle-stimulating hormone, adrenocorticotropic hormone and growth hormone. The release of these hormones is controlled by the hypothalamus. When stimulated, the hypothalamus secretes releasing hormones into the bloodstream and down the hypophyseal portal system to reach target receptors on the anterior pituitary. Once the releasing factors reach the anterior pituitary,

hormones stored are released into general circulation. These hormones either act directly on target tissues or act on other endocrine glands to stimulate the release of other hormones.

The hypothalamic pituitary adrenal (HPA) axis is an example of a system controlled by the hypothalamus and anterior pituitary gland. The first step of the HPA axis involves the paraventricular nucleus of the hypothalamus which releases corticotrophin-releasing hormone (CRH), which upon reaching the anterior pituitary stimulates the release of adrenocorticotropic hormone (ACTH) into the general circulation. ACTH reaches target cells at the adrenal gland and stimulates the release of cortisol into the bloodstream. Cortisol levels then interact with glucocorticoid or mineralocorticoid receptors on target cells throughout the body to modulate various cellular processes. The release of cortisol is controlled by a negative feedback system. Once cortisol concentrations rise beyond a certain threshold, they bind to receptors in the hypothalamus and anterior pituitary inhibiting further release of CRH and ACTH, respectively. There are other neural structures that exert either inhibitory (hippocampus, prefrontal cortex) or excitatory (amygdala) effects on the HPA axis.

In addition to this system, the hypothalamus can also communicate with the posterior region of the pituitary gland via direct neural connections through the hypothalamic-hypophyseal tract. This neural integration allows the hypothalamus to have direct communication with the posterior pituitary using it as a relay and storage station for two primary hormones it produces; oxytocin and arginine vasopressin (AVP). These two hormones are synthesized in magnocellular neurons in the paraventricular and supraoptic nuclei of the hypothalamus and stored in axon terminals located in the posterior pituitary. When the hypothalamus is stimulated it prompts the posterior pituitary to release its contents into the bloodstream. In addition to its peripheral release, there are also direct AVP and OT projections from the hypothalamus to several key brain regions including the amygdala, hippocampus, striatum, bed nucleus of the stria terminalis, and the brain stem (Meyer-Lindenberg et al., 2011). In the periphery, AVP plays a key role in water retention, while as we have seen, OT is important for promoting uterine contractions during childbirth and milk letdown during nursing. In the CNS, both hormones have been linked to cognitive, affective, and behavioral processes critical to survive and reproduction (Bartz et al., 2011: Meyer-Lindenberg et al., 2011).

Although numerous hormones are clearly implicated in the modulation of complex human social behavior, we now turn our attention to testosterone. We begin this section by reviewing two prominent theoretical models guiding current research on testosterone and intra-sexual competition: the ‘Challenge Hypothesis’ and the ‘Biosocial Model of Status’. We then describe research investigating the functional consequences of endogenous testosterone dynamics with a focus on aggressive, competitive, risk-taking, and mate-seeking behavior. Finally, we end the chapter with some speculation about the neural mechanisms through which testosterone may ultimately modulate human aggressive behavior.

TESTOSTERONE AND AGGRESSIVE BEHAVIOR

The idea that testosterone is linked to evolutionarily important behaviors such as aggression and reproduction has been known since the classic castration-replacement experiments performed by Arnold Berthold. Traditionally, research on the

neuroendocrine basis of aggressive behavior has taken a unidirectional approach focusing on testosterone's role in promoting aggression (Simon & Lu, 2006). However, studies of the relationship between baseline testosterone concentrations and aggressive behavior in people have yielded very small effects [r = .08](Archer, Graham-Kevan, & Davis, 2005). Importantly, however, competitive and aggressive interactions are known to potentiate testosterone release (Oliveira, 2009: Wingfield, Hegner, Dufty, & Ball 1990), suggesting that the relationship between testosterone and aggressive behavior is much more complex than previously thought. In fact, testosterone concentrations are highly responsive to competitive interactions in a number of taxa including birds (Wingfield et al., 1990), fish (Oliveira, 2009), non-human primates (Bernstein, Rose, & Gordon, 1974), humans (Archer, 2006), and insects (Scott, 2006). The following section will present an overview of this literature beginning with a description of the 'Challenge Hypothesis' and the 'Biosocial Model of Status', two of the main theoretical models guiding current research on the bidirectional relationship between testosterone and aggressive behavior.

Challenge Hypothesis

The ‘Challenge Hypothesis’ was originally developed to explain intra- and inter-species variation in testosterone secretion in birds. Wingfield et al. (1990) noted that testosterone concentrations fluctuate around three levels during the season: Level A, constitutive baseline; Level B, breeding baseline; and Level C, physiological maximum. In monogamous male birds that provide paternal care, testosterone concentrations remain low at Level A during the non-breeding season. Concentrations increase to Level B at the start of the breeding season as a means to initiate spermatogenesis, expression of secondary sex characteristics and the full display of male reproductive behavior. Finally, concentrations may further increase to Level C in response to intra-sexual competitive interactions as a means to facilitate aggressive behavior. When intra-sexual competition decreases, testosterone concentrations also decrease to Level A. It has been proposed that the costs associated with maintaining elevated testosterone concentrations throughout the season (e.g., decreased paternal care, increased risk for physical injury/death, depressed immune function, increased energetic demands) may have led to a highly flexible endocrine system capable of modulating testosterone concentrations in response to changes in the social environment (Wingfield, Lynn, & Soma, 2001). Although the ‘Challenge Hypothesis’ was originally proposed to account for hormone-behavior relationships in birds, its main hypotheses have received support in a number of taxa (Archer, 2006; Oliveira, 2009). The finding that some predictions derived from the 'Challenge Hypothesis' also apply to non-human primates (Cavigelli & Pereira, 2000) is particularly intriguing given that non-human primates are more closely related to humans.

Biosocial Model of Status

The ‘Biosocial Model of Status’ (Mazur, 1985) is a conceptually similar theoretical model to the ‘Challenge Hypothesis’. One important difference between the ‘Challenge Hypothesis’ and the ‘Biosocial Model of Status’ is that the latter makes the additional prediction that testosterone concentrations during competition will vary as a function of the outcome of the competitive interaction: Winners will experience an increase in testosterone, whereas losers will experience a decrease. Mazur (1985) reasoned that winners of competitive interactions may face additional challenges for status and that the increase in testosterone may serve to promote competitive and aggressive behaviors aimed at defending one’s status. In contrast, the decrease in

testosterone in response to defeat serves to promote submissive behaviors aimed at avoiding further loss of status and/or physical injury. Thus, from an evolutionary perspective, these divergent testosterone responses may enable organisms to adjust future social behavior according to changes in the social environment.

Although the 'Biosocial Model of Status' has mainly been studied within the context of human competition, its main predictions come from research conducted in male rhesus monkeys. In a series of experiments it was reported that aggressive interactions in male rhesus monkeys modulated testosterone release (Rose, Gordon, Bernstein, 1972: Rose, Bernstein, Gordon, 1975). Specifically, the authors found that male rhesus monkeys that were successful in aggressive interactions experienced marked elevations in testosterone, while unsuccessful males experienced decreased testosterone concentrations. Most current research testing hypotheses derived from the 'Biosocial Model of Status' comes from studies involving sport competitions (Salvador, 2005: Archer, 2006). Competitive sports provide an ideal environment in which to study hormone/behavior relationships as they have clear rules and regulations and offer the opportunity to study the effects of competition outcome and social context (home versus away; e.g., Carré, Muir, Belanger & Putnam, 2006: Carré, 2009) on testosterone concentrations. The first study in humans to demonstrate the effect of competition outcome on testosterone responses was based on a small sample of male university tennis players. The authors reported that men had an increase in testosterone after a victory and a decrease in testosterone after a defeat (Mazur & Lamb, 1980). A similar effect was observed in another small study of male university wrestlers in which winners had elevated post-competition testosterone concentrations relative to losers (Elias, 1981). Similarly, another study of male tennis players reported an increase in testosterone among winners relative to losers (Booth, Shelley, Mazur, Tharp, & Kittok, 1989).

The importance of the objective outcome in modulating testosterone release is corroborated by a recent study in male cichlid fish. In that study, the authors took advantage of the fact that cichlid fish cannot recognize their own image in a mirror, and as a result, attack their image vigorously as if the image were that of another fish. The authors reasoned that if aggressive behavior is the factor responsible for modulating testosterone release, then these fish should have an increase in testosterone in the 'mirror-challenge' condition (Oliveira, Carneiro, & Canario, 2005). In contrast, if the outcome of the interaction is critical to modulating testosterone release, then no testosterone change would be expected based on the fact that there was no clear outcome (i.e., it ended in a draw). Their results were consistent with the latter hypothesis; testosterone concentrations were non-responsive to the mirror elicited challenge, despite the finding that the fish increased their rate of aggressive behavior during the testing period (Oliveira et al., 2005).

One methodological limitation to research involving athletic competition is that physical activity is known to potentiate testosterone release (Kraemer & Ratamess, 2005). Therefore, it is possible that the greater increase in testosterone observed among winners relative to losers may be in part attributed to differential physical effort involved in victory versus defeat. In response to this methodological concern, several studies have examined the extent to which competition outcome would have divergent effects on testosterone release in non-physically taxing competitive tasks. Studies involving men engaged in reaction-time tasks, chess tournaments, dominoes, and coin toss competitions

have all reported that post-competition testosterone concentrations are elevated in winners relative to losers (Flinn, Ponzi, Muehlenbein, 2012: Gladue, Boechler, & McCaul, 1989; McCaul, Gladue, & Joppa, 1992). Notably, one study reported that winner/loser effects on testosterone responses did not occur when competing with one's 'ingroup', but did occur when competing with one's 'outgroup' (Flinn et al., 2012). The latter findings indicate that consideration of an opponent's group membership may be a critical variable to consider in future work. This nuance notwithstanding, the above findings indicate that changes in status after victory or defeat, rather than physical activity per se, may contribute to the differential testosterone responses observed.

Some studies suggest that the effect of competition outcome on testosterone release may occur in individuals not directly involved in the competitive interaction. Bernhardt, Dabbs, Fielden, and Lutter (1998) obtained pre and post- game saliva samples from male spectators attending college basketball and professional soccer games. Supporters of the winning and losing teams demonstrated an increase and decrease in testosterone, respectively. In a more recent series of studies, male varsity hockey players watched videos of themselves engaged in a previous victory, previous defeat, and/or a neutral documentary film. Saliva samples were collected prior to and at the conclusion of each video. Carré and Putnam (2010) reported that testosterone concentrations increased significantly after watching a video of a previous victory, but not after a defeat or a neutral video. A recent study has extended these findings to the political domain, reporting that men (but not women) who voted for John McCain the night of the 2008 US Presidential election had decreased testosterone concentrations after the vote, whereas those who voted for Barack Obama experienced no change in testosterone (Stanton, Beehner, Saini, Kuhn, & Labar, 2009). It is unclear why Obama voters did not experience a rise in testosterone. However, the differential testosterone response is consistent with the idea that the outcome of competition may influence the pattern of testosterone release (Mazur, 1985). A similar 'spectator effect' has been observed in male cichlid fish. In their experiment, Oliveira, Lopes, Carneiro & Camirio (2001) allowed fish to watch two isolated conspecific male neighbors through a one-way mirror. After a period of habituation, the opaque partition separating the two neighbors was removed, allowing the bystander fish to observe their neighbors engaged in an aggressive interaction. Results indicated that the experimental bystanders exposed to an aggressive interaction had significantly higher testosterone and 11-ketotestosterone (a metabolite of testosterone) concentrations relative to the control bystanders not exposed to an aggressive interaction. These studies provide support for the idea that simply watching competition can have similar effects on the neuroendocrine system as that observed when one actually engages in competition.

In summary, the literature reviewed above suggests that testosterone is highly responsive to competitive interactions and that winners typically have elevated testosterone concentrations relative to losers. Most of these results have been interpreted from a functional perspective whereby acute increases in testosterone may serve to promote competitive and aggressive behaviors. In the following section we review this evidence and also consider the possibility that in addition to competitive and aggressive behavior, acute increases in testosterone may also promote risk-taking and mate-seeking behaviors.

TESTOSTERONE DYNAMICS, COMPETITIVE MOTIVATION AND ATHLETIC PERFORMANCE

There is now a growing body of evidence in humans examining the extent to which acute changes in testosterone map onto future competitive motivation. In one experiment, Mehta and Josephs (2006) had men participate against each other in a rigged laboratory competition in which half were randomly assigned to a loss condition and half to a win condition. After the competition, participants were asked whether they wanted to compete again against the same opponent on the same task, or whether they would prefer to fill out a questionnaire on food, music and entertainment preferences (i.e., a measure of willingness to avoid competition). Mehta and Josephs (2006) reported that men demonstrating a rise in testosterone concentrations were more likely to choose to compete again, whereas men demonstrating a decrease in testosterone concentrations during the competition were more likely to choose the non-competitive option. Notably, this effect was significant in losers, but not winners. The authors attribute this outcome dependent effect to the fact that winners had nothing to gain from re-challenging the losers to another competition. In another study, Carré and McCormick (2008) collected saliva samples before and after participants played the Point Subtraction Aggression Paradigm (PSAP), a well-established behavioral measure of reactive aggression (Cherek, Tcheremissine, & Lane 2006). In this task, participants are led to believe that they are playing a computer game with another same-sex participant (in reality, this is a fictitious opponent). Here, participants must hit a button a hundred consecutive times to earn a point. Participants are told that their payment at the conclusion of the study will be based on the number of points they earn during the task, and thus, they are highly motivated to earn points. Throughout the task, points are stolen from participants and this is attributed to their fictitious opponent who gets to keep all the stolen points. Participants can respond by ignoring the provocation (i.e., continue earning points), by stealing points back, or by protecting their points from subtraction. Stealing points back is a costly behavior because participants do not get to keep the stolen points and engaging in such behavior detracts from points earned during the game. Stealing points in this game serves the function of retaliating against one's opponent, and thus, is considered a form of reactive aggression. After participants completed the PSAP, a second saliva sample was collected and participants were asked whether they want to compete with the same person on a puzzle-solving task or help the investigator validate a computer program assessing puzzle-solving abilities. Results indicated that an increase in testosterone predicted willingness to choose the competitive versus non-competitive option (Carré & McCormick, 2008).

Other work has investigated the extent to which acute changes in testosterone during motivational interventions would influence subsequent athletic performance and physical strength. Cook and Crewther (2012b) reported that athletes receiving positive feedback from their coaches prior to a competitive interaction demonstrated both a rise in testosterone concentrations and better athletic performance. In a subsequent study, the authors reported that watching motivational and aggressive video clips increased testosterone concentrations and improved subsequent physical strength as indexed by squat performance (Cook & Crewther, 2012a). Collectively, this small body of evidence suggests that acute fluctuations in testosterone may modulate competitive motivation and physical performance, perhaps through modulating neural mechanisms underlying competiveness and/or muscle physiology critical to athletic performance.

TESTOSTERONE DYNAMICS AND AGGRESSIVE BEHAVIOR

A larger body of evidence in both humans and non-human animal models has examined the extent to which acute fluctuations in testosterone may serve to modulate aggressive behavior. In one experiment, Klinesmith, Kasser and McAndrew (2006) randomly assigned men to interact with a toy gun or with a board game. The authors hypothesized that interacting with a toy gun would represent a 'challenge' and that in accordance with research on the effects of social challenge this would produce an increase in testosterone concentrations (e.g., Wingfield et al., 1990; Archer, 2006). After providing their second saliva sample (the first was provided before the interaction), participants were given a cup of water and were instructed to add as much, or little hot sauce to the cup, which would later be consumed by another participant. The amount of hot sauce placed in the cup served as the primary measure of aggression. As predicted, men who interacted with the toy gun demonstrated an increase in testosterone concentrations and were more aggressive. Critically, the relationship between interacting with the toy gun and aggressive behavior was statistically mediated by testosterone responses to the task.

In another experiment, Carré, Putnam, and McCormick (2009) had men and women compete in same-sex dyads on a rigged laboratory competition wherein half were randomly assigned to a win condition and half to a loss condition. After the competitive interaction, participants performed the PSAP with the same opponent. For men, a rise in testosterone during the competitive interaction predicted increased aggression in the subsequent interaction (Carré et al., 2009). Similar to Mehta and Josephs (2006), the effects of testosterone dynamics on aggressive behavior were most robust among male losers. In another study, we reported that changes in testosterone in response to social inclusion (but not social exclusion) were positively correlated with subsequent reactive aggression among men tested on the PSAP (Geniole, Carre, McCormick, 2011).

In more recent work, we modeled competition using an Xbox Kinect video game (Carré, Campbell, Lozoya, Goetz, & Welker, 2013). A relatively large sample of men and women (n = 237) were randomly assigned to experience a string of victories or defeats in either a boxing or a volleyball game. Results indicated that male winners had elevated testosterone concentrations and aggressive behavior compared to male losers. Moreover, the effect of winning on subsequent aggressive behavior was statistically mediated by heightened testosterone concentrations after the victory (Carré et al., 2013), providing the first complete support for the 'Biosocial Model of Status' as originally proposed by Mazur (1985).

Finally, we recently demonstrated that a long-term intervention program designed to curtail antisocial behavior in 'at-risk' youth was successful, in part, because it dampened testosterone responses to social provocation. This intervention was implemented in kindergarten and the children assigned to the intervention condition received social-cognitive-behavioral therapy, while those assigned to the control condition received no such treatment. When tested 20 years later, the intervention group demonstrated less aggression on the PSAP and decreased testosterone reactivity to social provocation compared to the control group. Notably, the association between assignment to the intervention condition and decreased aggression was statistically mediated by decreased testosterone reactivity to provocation (Carré, Iselin, Welker, Hariri, & Dodge,

in press). Collectively, these findings are consistent with the idea that acute fluctuations in testosterone within the context of human competition may have important effects on current and/or future social behavior. Notably, the effects of testosterone dynamics on aggressive behavior in the studies reviewed here were found exclusively in men (Carré et al., 2009; Carré et al., 2013). One clear limitation to this body of research is that it is correlational. Specifically, because we have not manipulated testosterone concentrations, it is not possible to make strong causal claims concerning testosterone's role in modulating competitive and aggressive behavior.

Animal research is particularly useful for testing causal mechanisms shaping complex social behavior. In recent experiments, administration of testosterone to male California mice after winning a competitive interaction produced increased aggressive behavior in subsequent interactions (Fuxjager et al., 2010: Gleason, Fuxjager, Oyegbile, & Marler, 2009; Trainor, Bird, & Marler, 2004) and increased their probability of winning subsequent interactions (Gleason et al., 2009; Fuxjager, Oyegbile, Marler, 2011). In addition, Oliveira, Silva, and Canario (2009) examined the role of testosterone in mediating the 'winner' and 'loser' effects in male tilapia. In control fish, winners of a first aggressive interaction were more likely to win a subsequent aggressive interaction (88% won second fight), whereas losers were more likely to lose subsequent interactions (87% lost second fight). Winners treated with an anti-androgen drug, which prevented the normal increase in testosterone in response to competitive interactions, were less likely to win a subsequent aggressive interaction (relative to control males). In contrast, losers treated with an androgen (11-ketotestosterone) were not more likely to win a subsequent aggressive interaction. These findings indicate that the 'winner effect' (but not the 'loser effect') depends critically on acute fluctuations in testosterone. In other work with male cichlid fish, unresolved social conflicts increased the probability of winning future competitive interactions – an effect that was in part due to heightened testosterone levels after the unresolved conflict (Dijkstra, Schaafsma, Hofmann, & Groothuis, 2012). Going beyond the role of circulating testosterone concentrations, Fuxjager and colleagues (2010) reported that the 'winner effect' was due to an up-regulation of androgen receptors in several key brain regions involved in reward and motivation (e.g., nucleus accumbens and ventral tegmental area) as well as social aggression (bed nucleus of the stria terminalis). Collectively, these experiments provide compelling support for the role of competition-induced testosterone dynamics in mediating ongoing and/or future social behavior. Moreover, the animal studies reviewed here are highly consistent with research in humans suggesting that competition-induced changes in testosterone may serve to modulate aggressive behavior.

TESTOSTERONE DYNAMICS, RISK-TASKING AND MATE-SEEKING BEHAVIOR

In addition to competitive motivation and aggressive behavior, recent work in humans has explored the role of context dependent fluctuations in testosterone in modulating risk-taking behavior. In a field study examining skateboarding performance in young men, Ronay and von Hippel (2010) found that men had elevated testosterone concentrations after interacting with an attractive female versus another male and subsequently engaged in more risk-taking behavior when performing dangerous skateboarding jumps. Notably, the association between interacting with the attractive

female and risk-taking behavior was statistically mediated by elevated testosterone concentrations. In another study, Carney, Cuddy and Yap (2010) randomly assigned men and women to hold brief dominant or submissive postures, after which they performed a risk-taking task. The authors reported that dominant postures increased testosterone concentrations and risk-taking behavior relative to submissive postures (Carney et al., 2010); however, it is unclear whether changes in testosterone mediated the effect of dominant postures on risk-taking behavior. In a more recent laboratory experiment, Apicella, Dreber, and Mollerstorm (2014) collected saliva samples prior to and at the end of a competitive interaction and then assessed risk preference in an economics task. The authors reported that men for whom testosterone concentrations increased in response to the competition were less risk averse compared to men for whom testosterone concentrations decreased. While the effects of testosterone dynamics on aggressive behavior appear to be specific to men (Carré et al., 2009; 2013), correlational (Stanton, Liening, & Schultheiss, 2011) and pharmacological challenge work (van Honk et al., 2004) indicates that testosterone is associated with risk-taking behavior in both men and women.

A separate body of work has examined testosterone responses among men interacting with potential mating partners. This work has revealed that men demonstrate a rapid increase in testosterone when interacting with attractive women (Roney, Mahler, & Maestripoeri, 2003: Roney, Lukaszewski, & Simmons, 2007: Roney, Simmons, & Lukaszewski, 2010). Moreover, changes in testosterone in response interacting with females were positively correlated with the extent to which men engaged in courtship behavior (Roney et al., 2003: 2007). Also changes in testosterone in men engaged in intra-sexual competition predicted increased mate-seeking behavior (van der Meij, Almela, Buunk, Fawcett, & Salvador, 2012). Other work suggests that even the scent of an ovulating woman rapidly increases testosterone concentrations in men (Cerda-Molina, Hernandez, de la O, Chavira-Ramierez, & Mondragon-Celballos, 2013: Miller & Maner, 2010: Roney & Simons, 2012). Notably, similar increases in testosterone have been observed in male mice and rats exposed to receptive females (Amstislavskaya & Popova, 2004) and in male common marmosets exposed to the scent of ovulatory females (Ziegler, Schultz-Darken, Scott, Snowdon, & Ferris, 2005). Moreover, rapid changes in testosterone concentrations increase the expression of copulatory behavior in house mice (James & Nyby, 2002). Thus, research in both humans and animal models suggest that acute changes in testosterone in response to brief exposure to potential mates (or the scent of potential mates), as well as competitive interactions, may serve to modulate risk-taking, mate-seeking and sexual behavior.

NEURAL CIRCUITRY UNDERLYING EFFECT OF TESTOSTERONE DYNAMICS ON AGGRESSION

A key question for future work will be to elucidate the neural mechanisms through which testosterone dynamics modulate human social behavior. Extensive work in animal models indicates that several inter-connected cortical and subcortical structures within the so-called social behavior network (Newman, 1999) are involved in the modulation of reactive aggression (Nelson & Trainor, 2007). One specific model that has received support from lesion and electrical/chemical stimulation experiments (mainly in rodents and cats) indicates that a neural circuitry comprising the medial amygdala, medial

hypothalamus and periaqueductal grey (PAG) positively modulates reactive aggression (Siegel, Bhatt, Bhatt, & Zalcman 2007). Briefly, the medial amygdala provides excitatory input to glutamatergic neurons in the medial hypothalamus, which exert excitatory drive on PAG neurons, ultimately mediating reactive aggression (Siegel et al., 2007; See Figure 1). Aggression research in human studies has focused mainly on the role of the orbitofrontal cortex (OFC). Specifically, many studies have reported that patients with localized lesions to the OFC engaged in heightened reactive aggression (Siever, 2008). Given the extensive projections from the OFC to the hypothalamus and amygdala, it has been proposed that the propensity to engage in reactive aggression may emerge from impaired regulatory control of the OFC over these subcortical structures (Nelson and Trainor, 2007).

One research approach aimed at elucidating the neurobiological mechanisms of human aggression examines behavioral and neural responses to angry facial expressions. Angry facial expressions represent honest signals of threat and, depending on the dominance relationship between sender and receiver, these threat stimuli may elicit fight or flight behavior from the receiver. Specifically, dominant individuals may perceive an angry facial expression as a challenge to their status, whereas submissive individuals may perceive the same angry facial expression as an enforcement of the prevailing relationship, thus promoting approach and avoidance behaviors, respectively (van Honk and Schutter, 2007). Behavioral and neuroimaging studies reported that individuals prone to anger and reactive aggression (e.g., intermittent explosive disorder, borderline personality disorder) displayed attentional biases, enhanced amygdala reactivity, and decreased OFC-amygdala coupling during processing of angry facial expressions, suggesting that such processes may represent a neurobiological marker for one's propensity to engage in reactive aggression (Siever, 2008). Studies in non-clinical samples reported that even normal variation in constructs linked to reactive aggression (e.g., approach motivation, trait anger, trait anxiety) mapped onto variability in amygdala reactivity to angry facial expressions. For instance, Beaver, Lawrence, and Passamonti (2008) reported that individual differences in approach motivation, a measure of one's relative sensitivity to rewards and a construct linked to reactive aggression (Harmon-Jones, 2003), were positively correlated with amygdala reactivity to angry facial expressions. Also, given that trait anger and trait anxiety are positively correlated with each other (van Honk, Tuiten, deHaan, van der Hout, & Stam, 2001) as well as with reactive aggression (Bettencourt, Talley, Benjamin, Valentine, 2006), we hypothesized that individuals high on both anxiety and anger would demonstrate amygdala hyper-reactivity to angry facial expressions. Consistent with this hypothesis, we found that individual differences in trait anger were positively correlated with amygdala reactivity to angry facial expressions, but only among men with relatively elevated trait anxiety scores (Carré, Fisher, Manuck, & Hariri, 2012). Other research has found that individual differences in approach motivation were associated with decreased ventral ACC-amygdala functional coupling during processing of angry facial expressions (Passamonti et al., 2009). Given the important role of highly interconnected prefrontal regions (e.g., ventral ACC, OFC) in mediating top-down regulation of amygdala driven emotional reactivity (Davidson, Putnam & Larson, 2000), such decreased functional coupling may, in part, explain the positive link observed between approach motivation and aggressive behavior (Harmon-Jones, 2003). Collectively, clinical and pre-clinical data converge on a

model in which relatively increased amygdala reactivity and/or decreased coupling of prefrontal regions (ventral ACC, OFC) with the amygdala during processing of threat-related stimuli may bias one's propensity to engage in reactive aggression (see Figure 1 for a review of some of this literature).

Importantly, androgen and estrogen receptors are widely distributed throughout the neural circuitry underlying reactive aggression (Newman, 1999), suggesting that testosterone and/or its metabolites (e.g., estradiol) may directly modulate this circuitry by interacting with intra-cellular androgen or estrogen receptors. Given the high concentration of androgen and estrogen receptors in the amygdala and related structures within the social behavior network, it is reasonable to predict that enhanced neural and behavioral reactivity to angry facial expressions may vary as a function of testosterone concentrations. Indeed, behavioral studies have reported that endogenous testosterone concentrations were positively correlated with attentional biases toward angry facial expressions (van Honk et al., 1999) and that exogenous testosterone administration increased cardiac responses to angry facial expressions (van Honk et al., 2001). Moreover, functional neuroimaging studies reported that individual differences in baseline testosterone concentrations were positively correlated with amygdala reactivity to facial expressions of anger and fear (Derntl et al., 2009; Manuck et al., 2010) and negatively correlated with OFC responses to perceived provocation (Mehta and Beer, 2010). Finally, exogenous administration of testosterone increased amygdala reactivity and decreased amygdala-OFC coupling during processing of angry facial expressions (Goetz et al., 2014: Hermans, Ramsey, van Honk, 2008: van Wingen et al., 2008: van Wingen, Mattern, Verkes, Buitelaar, Fernandez, 2010). More recently, we have reported that testosterone administration increases hypothalamic reactivity to angry, but not fearful or surprise expression in healthy young men (Goetz et al., 2014; See Figure 1). Thus, to the extent that enhanced behavioral and neural responses to social threat bias reactive aggression, the findings reviewed in this section suggest that testosterone may modulate the expression of reactive aggression by enhancing amygdala reactivity and/or decreasing ventral ACC/OFC-amygdala coupling during processing of social threat (e.g., angry facial expression, social provocation).

SUMMARY

Although hormones are secreted in relatively small quantities, they can have widespread influences on numerous physiological and behavioral processes. Here, we have reviewed human and non-human animal literature indicating that testosterone is implicated in competitive, aggressive, risk-taking, and mate-seeking behavior. Given the importance of such behaviors for survival and reproduction, it is perhaps not surprising that we find converging support for the role of testosterone dynamics in modulating such processes in human and non-human animals. Future research will benefit greatly by considering the neural mechanisms through which testosterone responses modulate behavior (e.g., Mehta & Beer, 2010) and by the use of novel pharmacological challenge paradigms (e.g., Goetz et al., 2014) designed to examine the extent to which testosterone plays a causal role in modulating human social behavior.

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Figure Legend

Figure 1. Neural circuitry underlying reactive aggression. Research in animal models indicates that the medial amygdala, medial hypothalamus and periaqueductal grey (PAG) positively modulates reactive aggression (Siegel, Bhatt, Bhatt, & Zalcman 2007). Here, the medial amygdala provides excitatory input to glutamatergic neurons in the medial hypothalamus, which exert excitatory drive on PAG neurons, ultimately mediating reactive aggression (Siegel et al., 2007). Neuroimaging results indicate a single administration of testosterone modulates this neural circuitry. Specifically, testosterone administration to young men rapidly increases amygdala, hypothalamus, and PAG reactivity to angry facial expressions (Goetz et al., in press). Figure redrawn based on Blair (2013). OFC = orbitofrontal cortex; PAG = periaqueductal grey.