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Commentary

Response to Wingfield's commentary on "A continuing saga: The role of testosterone in aggression"

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We thank Professor Wingfield for his commentary in this issue and the interesting questions he raises about the challenge effect and its functions in the control of aggressive behavior. He suggests several intriguing ideas that are worth pursuing, particularly in relation to the temporal nature of the testosterone (T) changes that occur in response to a competitive encounter. Testosterone changes can be short term, long term and the timing of the change can vary. Furthermore, some of these changes may be modulated by learning processes.

The idea of "persistence of aggression," as described by Wingfield (2005) and supported by research from his laboratory, covers several possible scenarios for temporal patterns of change in T. Testosterone implants alter T for longer periods of time and provide an excellent tool for manipulating hormones under field conditions. As Wingfield describes, the use of T implants nicely demonstrates how T extends the expression of aggression within an encounter, thereby increasing "persistence of aggression." Repeated T injections are not generally feasible under field conditions because of the difficulties in recapturing animals. Injections are, however, useful for testing how rapid transient increases in T can influence future behavior. The transient nature of the changes in T after an encounter in California mice, *Peromyscus californicus* is shown in Fig. 1. These results also suggest that there may be variation in the T pattern, as Oyegbile and Marler (2005) did not find a difference in T after a single aggressive encounter (for variation in transient T profiles see Amstislavskaya and Popova, 2004). The temporal pattern of changes in T in Fig. 1 was mimicked by Trainor et al. (2004) via injections and demonstrated that transient increases in T can also influence future aggression. Trainor et al. (2004) tested the idea developed in Oyegbile and Marler (2005) that link the "challenge" and "winner" effects. Those results further supported the general idea of "persistence of aggression" but, combined with the T-implant studies described by Wingfield, suggest that T can influence the persistence of aggression in different ways. One is to extend aggression in a current encounter; the other is to increase aggression in future encounters.

It remains to be seen whether T acts through similar mechanisms to influence different aspects of "persistence of aggression." Wingfield raises the issue of whether T is influencing persistence of aggression through estradiol or androgen receptors. In the California mice, transient increases in T combined with winning experiences influence future aggression via androgen and not estradiol receptor pathways (Trainor et al., 2004). However, baseline levels of aggression are at least partially dependent on estradiol-mediated pathways. An aromatase inhibitor decreased the baseline levels of aggression, but did not affect aggression changes observed in response to transient increases in T and the experience of winning. It is also possible that implants, and therefore possibly persistence of aggression after an encounter, may be acting through estrogen receptors. Thus, we agree with Wingfield that it will be very important to test how T influences these different aspects of aggression. Furthermore, we also need to consider that neural mechanisms unrelated to steroid hormones may be activated in aggressive encounters and then influence and interact in the

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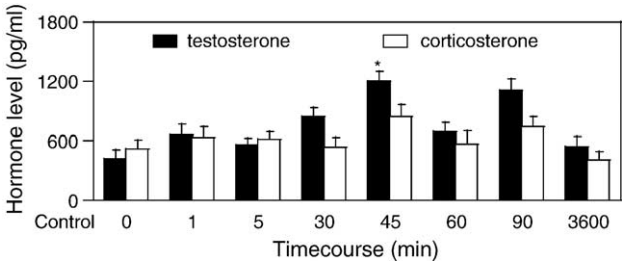

Fig. 1. The time course for changes in testosterone and corticosterone after a single aggressive encounter. The aggressive encounters were staged in an identical manner to those described in the Methods section of Oyegbile and Marler (2005). Blood samples were obtained by decapitation. A total of 56 male *P. californicus* mice were randomly assigned to eight groups ($n = 7$ per group). Blood samples were collected by decapitation at 0 min, 15 min, 30 min, 45 min, 60 min, 90 min and 24 h after an aggressive encounter. The 8th group served as a control group in which males experienced no aggressive encounter. Testosterone levels peaked at 45 min after an aggressive encounter, and univariate analysis revealed that this level was significantly different from the controls (overall ANOVA: $F(7,40) = 2.02$, $P = 0.216$; LSD comparing controls to 45 min sample: $P = 0.023$). There was no significant change in corticosterone levels (overall ANOVA: $F(7,40) = 0.89$, $P = 0.523$).

production of aggressive motor patterns both in current and future encounters. The relationship of T changes and aggressive experiences to the potential underlying mechanisms of emotion such as anger is also an intriguing area of potential research, particularly now that brain areas involved in anger, such as the medial orbitofrontal cortex, are being identified in humans using functional neuroimaging (Murphy et al., 2003).

The temporal pattern of T and the receptors upon which it acts represent two variations in how T might influence aggression. A third important factor that has remained largely unexplored is the interaction between conditioned learning and the challenge effect. For example, does T increase before an encounter? If so, some anticipatory learning must be involved. While most animal studies have focused on changes in T after an encounter, a variety of human studies find that T levels change prior to an encounter, that is, there is an anticipatory rise in T when there is going to be a sporting or competitive contest (e.g. Booth et al., 1989; Mazur et al., 1992; Neave and Wolfson, 2003; Suay et al., 1999). How this pre-encounter rise in T relates to the challenge effect and whether it is an extension of the challenge effect that is created through learning is unknown. Nevertheless, it may be that T increases prior to a competitive event in the human studies because these studies often involve an anticipatory component; individuals can predict when a sports challenge is going to occur, how critical the game is, etc. Furthermore, as Wingfield describes, T can also increase in individuals watching a sporting event (Bernhardt et al., 1998).

Several studies suggest that transient changes in T may act to reinforce learning associated with aggressive encounters. Research on steroid abuse suggests that T can have rewarding properties. Peripheral injections of T and central implants of T, dihydrotestosterone, or 3alpha-diol can induce a conditioned place preference (CPP) in rats (e.g. Alexander et al., 1994; Rosellini et al., 2001). Androgen-induced CPPs are blocked by dopamine receptor antagonists. (Packard et al., 1998; Schroeder and Packard, 2000), suggesting that T may activate dopamine receptors to create a reward and induce a CPP. Additional support indicating that T may act as a reinforcer comes from studies involving sexual behavior. Interestingly, the T profile shown in Fig. 1 is very similar to the profile observed when male mice are exposed to an estrous female behind a partition (Amstislavskaya and Popova, 2004). It is intriguing that males will also display conditioned place preferences in sexual contexts and these results have been linked with T (Alexander et al., 1994; Hughes et al., 1990; Wood, 2004). Based on the rewarding aspects of testosterone, we speculate that one function of the transient increase in T in winners may be to create a place preference (CPP) for that area and thereby influence territorial behavior. This raises the question of what is learned in an aggressive encounter, as well as what testosterone could reinforce and/or stimulate in the learning process. Besides influencing a place preference, there may also be learning related to the outcome of the encounter, whether the intruder was a winner or loser, the fighting skills of the intruder, the behavioral strategies used in the fight, and environmental cues that might predict prospects in future encounters.

Overall, we may be underestimating the plasticity in the challenge effect. Investigations into this plasticity may highlight new functions for the challenge effect. This becomes particularly relevant when investigating how T functions in the brain and how T changes are integrating with the paired behavioral experiences. The timing of the T change may also be very useful for separating out the potential functions of the T changes. The anticipatory T changes may influence behavior at the initiation of the encounter. In contrast, the T changes immediately after the encounter or during the encounter may (1) extend or maintain the current encounter or (2) influence establishment and consolidation of memories about details of the encounter and how that information is put to use in future aggressive interactions.

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