Commentary

Muscle, a conduit to brain for hormonal control of behavior

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ABSTRACT

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Investigation into mechanisms whereby hormones control behavior often starts with actions on central nervous system (CNS) motivation and motor systems and is followed by assessment of CNS drive of coordinated striated muscle contractions. Here we turn this perspective on its head by discussing ways in which hormones might first act on muscle that then secondarily drive upstream the evolution and function of the CNS. While there is a lengthy history for consideration of this perspective, newly discovered properties of muscle signaling reveal novel mechanisms that may well be captured by endocrine systems and thus of interest to behavioral endocrinologists.

1. Introduction

The vast majority of us who call ourselves behavioral endocrinologists often focus our research on the central nervous system (CNS), especially the brain. This might involve the way sensory and cognitive forces act via the brain to influence pituitary-based axes and the hormones they produce or it involves the way the CNS responds to hormones to influence the processing of sensory information, the motivation to behave, and the motor outputs whose patterning forms the basis of the hormone-dependent behavior.

Of course, a complete understanding of behavior requires an appreciation of the ways that neural circuits control striated muscles that, by their appropriate coordinated contractions, produce all the requisite postural, limb and accessory movements that together form true behavior. For behavior to arise then, selection must minimally shape the neural motor pathways, select skeletal muscles and their fibers and the proprioceptive sensory feedback circuits, from muscle to brain. Although we have been aware for many years that muscles themselves are targets of hormonal action, there is increasing evidence that muscles exert unique forms of control over the CNS that impact behavior. It may well be worth a second look at the striated muscles themselves and how they may modify the CNS in a retrograde or "muscle-up" fashion.

Here we present some lines of research that point to striated muscles as primary sites for guiding evolution (ultimate causation) and functions (proximate causation) of the CNS and behavioral performance. From the standpoint of hormonal action, we consider two cases that address ways in which androgens target striated muscles that in turn provide a basis, or potential basis, to drive upstream neural control systems and ultimately behavioral performance. First, we describe evidence for selection acting on androgen receptor (AR) expression in muscle as directly guiding the physical complexity underlying the performance of male courtship displays (ultimate causation). Second, we describe evidence from the well-studied spinal nucleus of the bulbocavernosus (SNB) system of rodents whereby androgen actions on muscles per se guide the development of upstream neural systems controlling muscle function (proximate causation).

By what mechanisms might hormones act on muscle to impact the brain? Whereas some mechanisms have been well-described, there are a surprising number of novel ways that muscle use or modified muscle gene expression promotes or modifies CNS function. Because we see this as an exciting emerging field, and one worthy of attention by behavioral endocrinologists, we focus the next section of this article describing some muscle-specific states that drive the CNS and several possible mechanisms that might be captured and utilized by hormones to influence behavior retrogradely. We start this section with a description of new evidence for how modified gene expression in skeletal muscle alone serves to regulate sleep-wake cycles. We conclude with a discussion of several newly identified pathways whereby muscles signal

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to the CNS to influence diverse brain states.

2. Hormonal control of male manakin courtship

We have considerable evidence that selection targeting the expression of androgen receptor (AR) in skeletal muscle is a pioneering event in the evolution of hormone-dependent courtship displays by at least some male vertebrates. Male golden-collared manakins (*Manacus vitellinus*) perform a courtship display that includes significant motor output including lengthy jumps created by contractions of muscles controlling the lower extremities, to powerful wing- and roll-snaps involving specialized contractions and coordinated movements of the upper extremities, all of which are combined with various postural movements and positioning (Schlinger et al., 2013). Many of the bird's individual movements are made at great speed. In most males, the movements are performed with exquisite precision, seen especially clearly when they are video recorded with ultra high-speed cameras (from 125 to 2000 frames per second) with images played back in slow motion (Barske et al., 2011).

This interesting bird belongs to a family of birds found in forests throughout the neotropics. Males of many of these species perform elaborate courtship displays as they engage in little to no parental care and can dedicate their time and energy to trying to attract females for copulations (Prum, 1990, 1994). Thus, physically intensive courtship displays are widespread in males of this clade. But they are not alone in this regard as other species from somewhat disparate bird groups also court females using interesting motor performances. Nevertheless, many of the manakins do stand out for their elaborate displays.

The underling neuromuscular substrate for the performance of complex courtship displays is just beginning to be investigated and understood. In the case of the golden collared manakin, we know that one muscle in particular seems specialized for the bird's ability to make their loud wing- and roll-snaps. Wingsnaps are produced singly, in mid-air, as the males jump from sapling to sapling around their display courts. Roll-snaps are produced as a rapid sequence of individual snaps with up to 23 snaps produced in ~300 msces (Fuxjager et al., 2013). These snaps can be heard for considerable distance through the forest and are produced, in all likelihood, to attract females to the male leks (Chapman, 1935). Snaps are produced as the wings are lifted by the supracoracoideus muscles, and then retracted by the scapulohumeralis (SH) muscles (Fuxjager et al., 2017a). This latter SH muscle is unusually enlarged and modified in this manakin (Lowe, 1942; Schultz et al., 2001), and is specialized to contract in an exceptionally fast manner (Fuxjager et al., 2017b).

Androgen action is crucial for performance of male manakin courtship (Day et al., 2006; Chiver and Schlinger, 2017a, b) with actions on skeletal muscles required for appropriate behavioral output. Androgen receptor antagonists that interfere with AR peripherally produce substantial deficits in male courtship (Fuxjager et al., 2013). Manakin skeletal muscles express AR at high levels (Feng et al., 2010) and androgens promote extensive modification in the cohort of genes expressed in forelimb muscles, with significantly greater impact on the SH muscle than on the PEC (Fuxjager et al., 2016). Inhibition of AR-dependent gene expression and muscle function specifically reduces contractile properties of the SH that underlie the muscle's participation in the creation of wing- and roll-snaps (Fuxjager et al., 2017b).

Whereas these data point to a central role for muscle AR function in steering the production of courtship behavior, they do not address the role of the CNS itself. While we do know that AR are expressed in brain of golden collared manakin in places that likely house pre-motor neurons that, when activated, produce the complex and highly coordinated set of behaviors that make-up courtship (Fusani et al., 2014), we know little about the central actions of androgen per se in influencing behavior. Presumably there is significant specialization of the manakin neural circuitry required to produce the behavior we observe in nature. Despite these limitations in the scope of our knowledge about CNS

control of male manakin behavior, we do have evidence that AR expression in skeletal muscle might be the key to the evolution of elaborate male courtship.

Across several species of birds with varying degrees of physical courtship, levels of AR expression in skeletal muscles, and not in the spinal cord, directly predict the complexity levels of that courtship (Fuxjager et al., 2015). Expression levels of ER had no bearing on courtship in muscle or in spinal cord. Moreover, expression levels of AR are independent of circulating testosterone levels as well as sex and age of the manakins (Fuxjager et al., 2018). All of these data support the notion that selection, presumably a result of female mate choice (Barske et al., 2011), has driven the evolution of increasing levels of AR and AR-responsivity specifically in muscle to promote the profound changes in gene expression required to produce contractile and metabolic states needed to produce complex behavior (Fuxjager et al., 2018).

Of course, there are other explanations and more data is needed to confirm this conclusion. Nevertheless, it stands at this point as a viable possibility, and lends support for the overall notion that selection for advanced AR signaling occurs first in muscle, and the neural circuits that drive specific muscles and the patterns of their contractile states arises as a secondary phenomenon. Muscles that are adapted for modified contraction might themselves communicate to central neural circuits acutely, by retrograde signaling, such as with growth factors (see below) or by other signaling mechanisms. Muscles with modified contractile states driven by unmodified neural circuits might produce behavior that is attractive to females. Once these contractile states become a target of female selection, further alteration of neural circuitry might arise to drive those muscles in ways that maximally stimulate the females to promote matings.

The manakin system we describe is not the only example where evolution might first act on peripheral musculature. Skeletal muscle AR expression and function is well-established in a variety of model systems (e.g. Zornik and Kelley, 2011). Muscles that contract to produce the unique foot-waving behavior of some species of frogs might have evolved AR expression first for this behavior to arise for use as an aggressive/territorial signal (Mangiamele et al., 2016). Similarly, AR expression in forelimb muscles of anolis lizards may also predict muscle function in courtship displays (Johnson et al., 2018). While these examples illustrate potential mechanisms for hormonal capture of some complex behaviors, it is indeed hard to imagine, for example, that the broad neural modifications that arose in songbirds to promote song and song learning developed secondarily to heightened AR expression and function in syringeal muscles (Veney and Wade, 2004). Nevertheless, AR are expressed and functional in syringeal muscles of suboscine as well as oscine songbirds (Veney and Wade, 2004; Feng et al., 2010; Fuxjager et al., 2014). Thus, AR expression in these muscles is likely an important target of selection that may form the basis of aspects of the evolution of the neural song system required for production of oscine birdsong.

The forces of selection on AR expression we describe above, point to androgen activation of muscles states to produce behavior. It stands to reason that for hormones to act on muscles to direct, upstream, the proper neural circuitry to drive behavior, that hormone action might occur developmentally. The well-established neuromuscular system controlling the bulbocavernosus muscle of rodents illustrates clearly how hormones act developmentally on AR-dependent muscle to create appropriate neural circuitry.

3. The SNB system

The SNB system has held profound and sustained interest for those studying sexual differentiation of the nervous system (Sengelaub and Forger, 2008; Swift-Gallant and Monks, 2017). There are a number of reasons for this, not least of which being that the SNB is methodologically tractable for site of androgen action studies. Here we discuss 2 main features of the SNB that are relevant for the present discussion: 1)