



Dynamic regulation of brain aromatase and isotocin receptor gene expression depends on parenting status

Ross DeAngelis^{a,b,*}, Logan Dodd^b, Amanda Snyder^b, Justin S. Rhodes^{a,b}

^a Program for Ecology, Evolution and Conservation Biology, University of Illinois at Urbana, Champaign, 405 N. Mathews Ave, Urbana, IL 61801, USA

^b Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana, Champaign, 405 N. Mathews Ave, Urbana, IL 61801, USA

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ABSTRACT

Fathering behavior is critical for offspring survival in many species across diverse taxa, but our understanding of the neuroendocrine mechanisms regulating paternal care is limited in part because of the few primarily paternal species among the common animal models. However, many teleosts display primarily paternal care, and among the teleosts, anemonefish species are particularly well suited for isolating molecular mechanisms of fathering as they perform parental care in isolation of many other typically competing behaviors such as territorial defense and nest building. The goal of this study was to determine the extent to which whole brain gene expression levels of isotocin receptors, arginine vasotocin receptors, and aromatase as well as circulating levels of the bioactive sex steroid hormones estradiol (E2) and 11-ketotestosterone (11KT) vary in association with parenting behavior in *Amphiprion ocellaris*. Brain aromatase and IT receptor gene expression were higher in both males and females that were parenting versus not. IT receptor expression was overall higher in males than females, which we interpret is a reflection of the greater parental effort that males display. Aromatase was overall higher in females than males, which we conclude is related to the higher circulating E2, which crosses into the brain and increases aromatase transcription. Results suggest both aromatase and IT receptors are dynamically upregulated in the brains of *A. ocellaris* males and females to support high levels of parental effort.

1. Introduction

Given the diverse and environmentally dependent nature of sociality, individuals are often required to make rapid and dynamic behavioral shifts within their social groups in a sex specific manner. As social circumstances and group dynamics vary, individuals must find ways to modify their behavior in order to maximize their fitness within the social structure (Lema et al., 2015; O'Connell and Hofmann, 2011; O'Connell and Hofmann, 2012). Understanding how species and sex specific behaviors are coordinated among, and within individuals is of keen interest in social neuroscience, especially as behavioral variation corresponds to variation within the brain (Goodson, 2008; Lee et al., 2009; Okhovat et al., 2015; Olazabal and Young, 2006). One such example of a stark behavioral shift is parental care. In contrast to maternal care, where pregnancy or gravidity induce a suite of physiological and hormonal changes prior to parturition or egg laying, physiological cues to fathers are more subtle. Notwithstanding the physiological subtleties priming fathers to care, fatherhood is often critical for offspring survival. Of course human males father, and this behavior is displayed in a highly variable way. Consequently, fatherhood has recently become a

highly socially relevant topic (Bales and Saltzman, 2016; Saltzman and Ziegler, 2014).

One obstacle that has limited our understanding of fathering behavior is the paucity of primarily paternal species among the common animal models. In mammals, male care is rare, and when it does occur, is often accompanied by active courtship and nest building. These preceding behaviors may modify the brain prior to parental care (Dulac et al., 2014; Wang et al., 1999; Young et al., 2005). This combination makes disentanglement of the underlying neural substrates for parental behavior challenging. Compared to mammals, male care is more common among teleost fishes. Recent findings in fish models have broadened our understanding of the neuroendocrine regulation of fathering behavior in vertebrates by showing that paternal care shares certain features in common with maternal care, such as the prominent role of isotocin signaling. Conversely, novel features such as the role of steroidogenesis within the brain have also been discovered (Deangelis et al., 2017; Deangelis and Rhodes, 2016; Kleszczyńska et al., 2012; Knapp et al., 1999; Kulczykowska and Kleszczyńska, 2014; O'Connell et al., 2012; Pradhan et al., 2014; Rodgers et al., 2006).

The nonapeptides arginine vasopressin (AVP) and oxytocin (OT), as

* Corresponding author at: Beckman Institute, 405 N. Mathews Ave, Urbana, IL 61801, USA.
E-mail address: Ross.DeAngelis@gmail.com (R. DeAngelis).

well as their non-mammalian homologs arginine vasotocin (AVT) and isotocin (IT), have been implicated as key neuromodulators in a variety of social behaviors, including parental care (Bales et al., 2004; Deangelis et al., 2017; Feldman et al., 2010; Gubernick et al., 1995; Insel and Young, 2000; Kozorovitskiy et al., 2006; Kulczykowska and Kleszczyńska, 2014). AVP/AVT and OT/IT neuron cell bodies reside primarily within the preoptic area of the hypothalamus (POA), and project widely throughout the brain (Goodson, 2008; O'Connell et al., 2012; Olazábal et al., 2013; Rosenblatt and Ceus, 1998). Furthermore, these nonapeptide signaling processes have often been cited as functioning in a sex specific manner. For example, the AVP signaling system underlies pair bonding more prominently in male prairie voles, while in female voles OT signaling pathways play a more important role (Young and Wang, 2004). Hence it is possible, if not likely, that these systems operate differentially in males and females with respect to parental care.

Cumulative evidence suggests that the nonapeptide neurons themselves are modulated, in part by sex steroid hormones, which bind to nuclear receptors and thereby alter gene expression. For example, in the California mouse, local action of brain aromatase, which converts testosterone (T) into estradiol (E2), is critical for high levels of paternal care (Trainor and Marler, 2001, 2002). Teleost fishes have higher brain aromatase activity than any other vertebrate group which may facilitate high levels of fathering behavior in this taxon (Forlano et al., 2001). One important hypothesized function of elevated brain E2 is upregulation of nonapeptide signaling via interactions with E2 nuclear receptors within nonapeptide neurons. E2-nuclear receptor interactions can alter gene transcription in nonapeptide neurons in a way that augments their function (Gimpl and Fahrenholz, 2001). In addition to regulating the synthesis of the nonapeptides within POA neurons, E2 facilitates the production of OT receptors throughout the brain in rats (Tribollet et al., 1990), and increases OT receptor binding in the pre-optic area and lateral septum at the onset of parenthood in female rodents (Champagne et al., 2001). Taken together these findings suggest that local conversion of T to E2 within the brain, or E2 from circulation that crosses into the brain play an important role in OT signaling, and in the regulation of parental care. However, whether the function of brain aromatase activity is conserved independent of sex and across species in the regulation of parental care remains unclear.

Compared to the functional role of E2 in the brain, the role of the bioactive androgens in regulating nonapeptide neurons and signaling systems involved in fathering behavior is far less understood. In the blue banded goby, conversion of T to 11KT within the brain is critical for high levels of male parental care (Pradhan et al., 2014), and in the bluegill sunfish, blockade of androgen receptors decreases nest defense (Dey et al., 2010). However, we have previously shown that circulating 11KT did not vary across the breeding cycle in male anemonefish, suggesting a minimal or non-existent role of circulating 11KT in fathering (Deangelis and Rhodes, 2016). So while some minimum level of androgens may be necessary for males to display paternal care, additional molecular substrates are likely responsible for the shift from non-parental to parental behavior. Taken together, the current literature suggests fathering behavior is mediated by increased OT/IT signaling via E2 aromatized from T locally within the brain, with minimal contributions from circulating bioactive sex steroids. However, the extent to which aromatase and IT/OT receptor gene expression are dynamically upregulated in male brains as they transition from inactive to active fathers remains unknown. Moreover, how these signaling pathways are either conserved across sexes, or function in a sex specific manner remains unclear.

In contrast to OT, the functional role of AVP/AVT signaling in the regulation of parental care is less understood. However, some recent studies have shown AVP as an important regulator of fathering behavior, nest defense, and territoriality. In prairie voles, AVP injections into the lateral septum, a brain region known to be involved in mediating behavioral acts related to offspring care, enhanced paternal care (Dulac

et al., 2014; Wang et al., 1994), and in the California mouse, AVP mRNA levels in the paraventricular hypothalamic nucleus correlated positively with the number of paternal behaviors displayed (De Jong et al., 2012). Similarly in pipefishes, AVT peptide concentrations are higher in the brains of parenting males vs. non-parenting males (Ripley and Foran, 2010). And in sticklebacks AVT peptide concentrations in the whole brain were highest in aggressive males actively caring for eggs (Kleszczyńska et al., 2012). While these studies suggest AVP/AVT signaling is important in paternal care, the specificity of the relation to offspring care as compared to involvement in aggression and territorial defense is less clear, as multiple behaviors occurred simultaneously in these animal models.

Among teleosts, the anemonefish *Amphiprion ocellaris* presents an exciting opportunity for exploring neuroendocrine regulation of male parental care. *A. ocellaris* lives in relatively small and simple social groups, where pair bonds and social hierarchies are established long before mating occurs. Therefore, there is no active courtship, nest building or intraspecific aggressive interactions co-occurring during high levels of parental care, enabling the underlying regulatory mechanisms to be more specifically extricated (Deangelis et al., 2017; Deangelis and Rhodes, 2016; Iwata et al., 2012; Iwata et al., 2010). Additionally, comparing brains of males and females that are actively parenting to those, which are not actively parenting, allows isolation of the molecular mechanisms regulating parental care.

We have recently shown that in *A. ocellaris*, blockade of IT receptors significantly reduces paternal care, whereas blockade of AVT V1a receptors increases fathering behavior (Deangelis et al., 2017). In a previous report we also documented that circulating E2 varies over the breeding cycle in females, but not males (Deangelis and Rhodes, 2016). Therefore, we hypothesized that circulating sex steroids (at least E2 in females), brain aromatase, AVT receptor V1a, and IT receptor gene expression would dynamically change as individuals shift in status between parenting and non-parenting. More specifically, we hypothesized that brain aromatase gene expression levels would increase in response to parental care in males, but still display relatively higher levels in females, due to positive feedback regulation by circulating E2 (Callard et al., 2001; Menuet et al., 2005). Further, we hypothesized that IT receptor gene expression would be higher in individuals actively caring for eggs compared to non-active parents. We expected that IT receptor gene expression would be higher in males than females, as a reflection of their higher levels of parental behavior. Finally, we hypothesized that AVT V1a receptor gene expression would show the opposite pattern, lower in parenting individuals and lower in males compared to females, based on the pharmacology result where blockade of V1a increased parenting in males. The goal of this study was to determine the extent to which brain aromatase, AVT V1a receptor, and IT receptor gene expression vary within the context of parenting and in relation to circulating bioactive sex steroid hormone levels, E2 and 11KT.

2. Materials and methods

2.1. Animals and husbandry

All fish used were offspring bred in house from broodstock obtained from ORA (Oceans Reefs and Aquariums, Fort Pierce, FL). Fish were kept in 20-gallon tall aquariums (24" × 12" × 16") integrated via plumbing to a large circulating filtration system. Conditions were set to mimic the natural environment with a pH between 8.0 and 8.4, temperature range of 79–82 °F, photoperiod of 12:12 (lights on at 7:00 am and off at 7:00 pm), and specific gravity of 1.026. All procedures were approved by the University of Illinois Institutional Animal Care and Use Committee.

Fish were kept in either one of two social housing conditions. First, animals were kept in pairs, containing one dominant female and one subordinate male. Each tank containing one 6" terra-cotta pot, serving

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