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SYMPOSIUM

Neurohormones, Brain, and Behavior: A Comparative Approach to Understanding Rapid Neuroendocrine Action

Rebecca M. Calisi[1,*] and Colin J. Saldanha[†]

*Department of Biology, Barnard College, Columbia University, New York, NY 10027, USA; †Department of Biology, American University, Washington, D.C. 20016, USA

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[1]E-mail: rcalisi@barnard.edu

Synopsis The definition of a hormone has been in part delineated by its journey to distant receptor targets. Following activation of a receptor, a subsequent reaction facilitates the regulation of physiology and, ultimately, behavior. However, a growing number of studies report that hormones can influence these events at a previously underappreciated high speed. With the potential to act as neurotransmitters, the definition of a hormone and its mechanisms of action are evolving. In this symposium, we united scientists who use contemporary molecular, electrophysiological, and biochemical approaches to study aspects of rapid hormone action in a broad array of systems across different levels of biological organization. What emerged was an overwhelming consensus that the use of integrative and comparative approaches fuels discovery and increases our understanding of *de novo* hormone synthesis, local actions of neurohormones, and subsequent effects on neuroplasticity and behavior.

Introduction

In 1849, Arnold Berthold reported that castrated cockerels behaved differently compared with their intact conspecifics. He also replaced testes into the abdominal cavity of castrated animals, an act that he found restored their normal behavior. This discovery catalyzed the field of behavioral endocrinology. Over a century later, a principle focus of this field remains the hormonal facilitation and mediation of behavior. A large volume of work has accumulated on how secreted signals can affect the brain and an impressive range of behaviors. Along the way, studies have noted that hormones can also work quickly, in manners tantalizing and inconsistent with the current appreciation of neuroendocrine processes. However, an enormous gap in understanding lies in how hormones influence rapid changes in behavior, and how these behavioral changes are modulated by mechanisms of hormonal provision and of response to hormones.

Locally generated neurohormones can have acute and chronic effects on several neurophysiological endpoints, including behavior. The recent literature on neuroendocrinology is rife with examples of the rapidity of synthesis and release of hormones within the central nervous system. For example, there now exists evidence of the action of local neurosteroids in every class of vertebrate, along with compelling evidence that synthesis of neurohormones can be rapidly regulated by environmental and endogenous factors. Understanding how neurohormones can alter the function of specific areas of the brain, as well as modulate the flow of information among areas of the brain, will shed light on downstream consequences for sensorimotor integration, behavior, and ultimately evolution. This symposium drew on exciting work currently being conducted in multiple systems in the laboratory and field on *de novo* hormone synthesis, local actions of neurohormones, and subsequent effects on animal behavior, such as those associated with reproduction, stress, sociality, seasonality, learning, and even epilepsy.

A highlight of this symposium was the importance of understanding how rapid provision of and response to estrogens in the brain can mediate behavior. Recent evidence implicates hormones such as estrogens may also share important characteristics of classical neurotransmitters (Remage-Healey et al. 2011; Remage-Healey 2012). For example, studies have localized the estrogen-synthetic enzyme, aromatase, to the synapse (Peterson et al. 2005; Rohmann et al. 2007), suggesting a role for synaptic provision of estrogen in neurotransmission. Remage-Healey et al. (2010, 2012, 2013) have used an *in vivo* retrodialysis technique to directly assess the rapid effect of estrogens on an auditory processing region in the brain of a male zebra finch (*Taeniopygia guttata*). They found that inhibition of estrogen production rapidly affected behavioral responses to song, suggesting a crucial role of neuroestrogen synthesis in sensory encoding and behavioral response (Saldanha et al. 2011). Evidence from wild-caught, seasonally breeding European starlings (*Sturnus vulgaris*) suggest that these effects have the potential to change according to photoperiod and reproductive state (Calisi et al. 2013), prompting further query into how real-world scenarios have affected the adaptation and application of this system.

Cornil et al. (2012) reported that it is synaptosomal, not microsomal, aromatase that appears to be rapidly modulated by ionic flux and phosphorylation. Hence, processes akin to synaptic currents may affect synaptic aromatization and thus synaptic transmission. Indeed, inhibition of local aromatization in the passerine hippocampus, an area rich in synaptic aromatase expression, but poor in somal expression, impairs spatial memory function in male finches (Bailey et al. 2013). It is also possible that rapid responses to estrogens may critically modulate behavior. For example, Maney reported that the expression of estrogen receptor alpha, encoded by ESR1 might drive a behavioral polymorphism found in white-throated sparrows (*Zonotrichia albicollis*) (Horton et al. 2014a, 2014b).

European starlings have served as a powerful model for investigating the neural underpinnings of behavior. Riters presented data collected from male starlings that, in response to acquiring a nest box during their breeding season, experience a rapid change (within minutes to hours) in courtship vocalizations. These changes are associated with a rapid increase in testosterone and its effect on androgen receptors in the preoptic nucleus (Alger and Riters 2006; Riters and Alger 2011). Riters pointed to mu-opioid receptor activity as a mechanism by which testosterone in the preoptic nucleus may rapidly affect courtship vocalization (Riters 2010; Kelm-Nelson and Riters 2013). Acquisition of nest boxes by European starlings is also associated with a reduction in activity of the hypothalamic neuropeptide gonadotropin inhibitory hormone (GnIH) when compared with starlings without nest boxes (Calisi et al. 2011; N. Amorin and R.M. Calisi, submitted for publication). As GnIH can have an inhibitory effect on the hypothalamic–pituitary–gonadal axis, its decreased activity may facilitate reproductive-associated behaviors (Calisi et al. 2008, 2011; Calisi 2014; Ubuka et al. 2014).

Environmental stressors can affect these reproductive behaviors. Dickens has been investigating the role aromatase, a key enzyme responsible for the biosynthesis of estrogens, plays in suppressing the sexual behavior of Japanese quail (*Coturnix japonica*). She and colleagues reported that acute stress and sexual interactions rapidly (less than 5–15 min) alter the activity of brain aromatase, and the region of influence and timeframe of change can be sex-specific (Dickens et al. 2011; de Bournoville et al. 2013). However, Dickens posited that by only using aromatase activity as a proxy for mechanisms involving estradiol, we may not be comprehending the full effects of the regulation of estradiol. Data she presented highlighted a catabolic pathway—the endocannabinoid system—as a potential rapid modulator of the stress response, although in birds this system has yet to be fully characterized.

Other steroidogenic enzymes are also potential candidates for the study of the rapid regulation of behavior. For example, Pradhan and Soma reported in 2010 that production of 3-beta-hydroxysteroid dehydrogenase/Delta 5-Delta 4-isomerase (3-beta-HSD), which eventually yields androstenedione in the brain, responds rapidly (<10 min) to acute stress in adult zebra finches and song sparrows (*Melospiza melodia*). 3-beta-HSD can also respond rapidly (<30 min) to a territorial encounter in male song sparrows. Soma presented further work on the acute and chronic effects of locally-synthesized steroids and their potential to act via both genomic and non-genomic mechanisms (Heimovics et al. 2012; Prior et al. 2014).

The idea that rapid alterations in the provision of hormones can affect neuronal function and behavior is not limited to birds. Woolley demonstrated the acute modulation of synaptic currents by estradiol and a role for estrogens, synthesized in the rat hippocampus, on neuronal excitability (Smejkalova and Woolley 2010; Huang and Woolley 2012; Tabatadze et al. 2013; May et al. 2014). These effects are not modest. Alterations in neuronal excitability appear to directly translate into seizures at the behavioral level, underscoring the dramatic role of neurally synthesized hormones in the brain and in behavior.

Bergan, inspired by the real-world adaptations of the avoidance of predators has been investigating the mechanisms of information-processing by the vomeronasal system. He and colleagues (2014) reported that sex-specific and species-specific responses in the mouse medial amygdala can rapidly alter sexual behavior in hormone-dependent and sex-specific manners. Additionally, they found that the development of such circuits is dependent on organizational effects by steroid signaling at about the time of puberty (Bergan et al. 2014).

Perhaps the most dramatic evidence of rapid changes within the arena of socially-driven, hormone-dependent neural physiology comes from studies in fish, like cichlids (*Astatotilapia burtoni*), bluehead wrasses (*Thalassoma bifasciatum*), and zebrafish (*Danio rerio*). Both Maruska and Godwin provided evidence of transformations in neurophysiology and behavior occurring minutes after removal of dominant morphs or males (Godwin 2010; Semsar and Godwin 2003, 2004; Maruska and Fernald 2010, Marsh-Hunkin et al. 2013; Maruska et al. 2013a, 2013b; Maruska 2014). While other hormone-dependent changes can take longer, the fact that aggressive and reproductive behaviors can change within minutes during transitions in social context generates many questions as to how behaviors we know to be hormone-dependent can be modulated independently of changes in signals of circulating hormones.

Conclusion

Hormones have long been thought of as chemical signals secreted from various glands in the body, which, via passage through the vasculature, take a reasonably long time to reach their distant target tissues. There they regulate processes like gene expression and morphological change. Given the extended temporal framework of hormonal action, a question has arisen: what then mediates rapid shifts in hormonally-regulated behavior? The ability of hormones to act acutely has been known for some time, but only recently have the finite processes by which these effects occur come into focus. This symposium highlighted this fundamental shift in our appreciation of the spatial and temporal precision of hormonal action. Hormones can be produced locally at the area of their action, even at individual neural synapses, and therefore would not require passage in blood to have a rapid effect on behavior. The turtle seems to have morphed into the hare! By uniting a diverse group of scientists who study a broad array of systems using different techniques across a range of behavioral endpoints, new lines of investigation emerged. This comparative approach offers promise for increasing our understanding of the rapid modulation of neuroendocrine action.

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References

Alger SJ, Riters LV. 2006. Lesions to the medial preoptic nucleus differentially affect singing and nest box-directed behaviors within and outside of the breeding season in European starlings (*Sturnus vulgaris*). Behav Neurosci 120:1326–36.

Bailey DJ, Ma C, Soma KK, Saldanha CJ. 2013. Inhibition of hippocampal aromatization impairs spatial memory performance in a male songbird. Endocrinology 154:4707–14.

Bergan JF, Ben-Shaul Y, Dulac C. 2014. Sex specific processing of social cues in the medial amygdala. Elife 3:e02743.

Calisi RM. 2014. An integrative overview of the role of gonadotropin inhibitory hormone in behavior: applying Tinbergen's four questions. Gen Comp Endocrinol 203:95–105.

Calisi RM, Díaz-Muñoz SL, Wingfield JC, Bentley GE. 2011. Social and breeding status are associated with recently discovered GnIH. Genes Brain Behav 10:557–64.

Calisi RM, Knudsen DP, Krause JS, Wingfield JC, Gentner TQ. 2013. Estradiol differentially affects auditory recognition and learning according to photoperiodic state in the adult male songbird, European starling (*Sturnus vulgaris*). PeerJ 1:e150–18. (doi:10.7717/peerj.150).

Calisi RM, Rizzo NO, Bentley GE. 2008. Seasonal differences in hypothalamic EGR-1 and GnIH expression following capture-handling stress in house sparrows (*Passer domesticus*). Gen Comp Endocrinol 157:283–7.

Cornil CA, Leung CH, Pletcher ER, Naranjo KC, Blauman SJ, Saldanha CJ. 2012. Acute and specific modulation of presynaptic aromatization in the vertebrate brain. Endocrinology 153:2562–67.

De Bournoville C, Dickens MJ, Ball GF, Balthazart J, Cornil CA. 2013. Dynamic changes in brain aromatase activity following sexual interactions in males: where, when and why? Psychoneuroendocrinology 38:789–99.

Dickens MJ, Cornil CA, Balthazart J. 2011. Acute stress differentially affects aromatase activity in specific brain nuclei of adult male and female quail. Endocrinology 152:4242–51.

Godwin J. 2010. Neuroendocrinology of sexual plasticity in teleost fishes. Front Neuroendocrinol 31:203–16.

Heimovics SA, Prior NH, Maddison CJ, Soma KK. 2012. Rapid and widespread effects of 17 beta-estradiol on intracellular signaling in the male songbird brain: a seasonal comparison. Endocrinology 153:1364–76.

Horton BM, Moore IT, Maney DL. 2014a. New insights into the hormonal and behavioural correlates of polymorphism in white-throated Sparrows. Anim Behav 93:207–19.

Horton BM, Hudson WH, Ortlund EA, Shirk S, Thomas JW, Young ER, Zinzow-Kramer WM, Maney DL. 2014b. Estrogen receptor α polymorphism in a species with alternative behavioral phenotypes. Proc Natl Acad Sci USA 111:1443–8.

Huang GZ, Woolley CS. 2012. Estradiol suppresses inhibition in the hippocampus through a sex-specific endocannabinoid and mGluR-dependent mechanism. Neuron 74:801–8.

Kelm-Nelson CA, Riters LV. 2013. Curvilinear relationships between mu-opiod labeling and undirected song in male European starlings (*Sturnus vulgaris*). Brain Res 1527:29–39.

Marsh-Hunkin ME, Heinz HM, Hawkins MB, Godwin J. 2013. Estrogenic control of behavioral sex change in the bluehead wrasse, *Thalassoma bifasciatum*. Integr Comp Biol 53:951–9.

Maruska KP. 2014. Social regulation in male cichlid fishes. Gen Comp Endocrinol 207:2–12.

Maruska KP, Fernald RD. 2010. Behavioral and physiological plasticity: rapid changes during social ascent in an African cichlid fish. Horm Behav 58:230–40.

Maruska KP, Becker L, Neboori A, Fernald RD. 2013a. Social descent with territory loss causes rapid behavioral endocrine and transcriptional changes in the brain. J Exp Biol 216:3656–66.

Maruska KP, Zhang A, Neboori A, Fernald RD. 2013b. Social opportunity causes rapid transcriptional changes in the social behavior network of the brain in an African cichlid fish. J Neuroendocrinol 25:145–57.

May RM, Tabatadze N, Czech MM, Woolley CS. 2014. Estradiol regulates large dense core vesicles in the hippocampus of adult female rats. Brain Struct Funct 219:1947–54.

Peterson RS, Yarram L, Schlinger BA, Saldanha CJ. 2005. Aromatase is pre-synaptic and sexually dimorphic in the adult zebra finch brain. Proc R Soc B Biol Sci 272:2089–96.

Prior NH, Yap KN, Soma KK. 2014. Acute and chronic effects of an aromatase inhibitor on pair-maintenance behavior of water-restricted zebra finch pairs. Gen Comp Endocrinol 196:62–71.

Remage-Healey L, Coleman ME, Oyama RK, Schlinger BA. 2010. Brain estrogens rapidly strengthen auditory encoding and guide song preference in a songbird. Proc Natl Acad Sci USA 107:3852–7.

Remage-Healey L, Saldanha CJ, Schlinger BA. 2011. Estradiol synthesis and action at the synapse: evidence for "synaptocine" signaling. Front Neuroendocrine Sci 2:1–13.

Remage-Healey L. 2012. Brain estrogen signaling effects acute modulation of acoustic communication behaviors: a working hypothesis. Bioessays 34:1009–16.

Remage-Healey L, Dong SM, Chao A, Schlinger BA. 2012. Sex-specific, rapid neuroestrogen fluctuations and neurophysiological actions in the songbird auditory forebrain. J Neurophysiol 107:1621–31.

Remage-Healey L, Jeon SD, Joshi NR. 2013. Recent evidence for rapid synthesis and action of estrogens during auditory processing in a songbird. J Neuroendocrinol 25:1024–31.

Riters LV. 2010. Evidence for opiod involvement in the motivation to sing. J Chem Neuroanat 39:141–8.

Riters LV, Alger SJ. 2011. Hormonal regulation of avian courtship and mating behaviors. In: Norries DO, Lopez KH, editors. Hormones and reproduction of vertebrates, Vol. 4. Academic Press, San Diego: Elsevier Science & Technology Books. p. 153–80.

Rohmann KN, Schlinger BA, Saldanha CJ. 2007. Subcellular compartmentalization of aromatase is sexually dimorphic in the adult zebra finch brain. Dev Neurobiol 67:1–9.

Saldanha CJ, Remage-Healey L, Schlinger BA. 2011. Synaptocrine signaling: steroid synthesis and action at the synapse. Endocr Rev 32:532–49.

Semsar K, Godwin J. 2003. Social influences on the arginine vasotocin system are independent of gonads in a sex-changing fish. J Neurosci 23:4386–93.

Semsar K, Godwin J. 2004. Multiple mechanisms of phenotype development in the bluehead wrasse. Horm Behav 45:345–53.

Smejkalova T, Woolley CS. 2010. Estradiol acutely potentiates hippocampal excitatory synaptic transmission through a presynaptic mechanism. J Neurosci 30:16137–48.

Tabatadze N, Smejkalova T, Woolley CS. 2013. Distribution and posttranslational modification of synaptic ER alpha in the adult female rat hippocampus. Endocrinology 154:819–30.

Ubuka T, Son YL, Tobari Y, Narihiro M, Bentley GE, Kriegsfeld LJ, Tsutsui K. 2014. Central and direct regulation of testicular activity by gonadotropin inhibitory hormones and its receptor. Front Endocrinol 5:1–10.