Reproductive Physiology: Songbird Study Removes Long-Standing Neuroendocrinology Research Roadblock

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Songbirds have long been favored as models to investigate the neuroendocrine mechanisms that regulate seasonal reproduction. Progress in this area has for many years been hindered by our inability to identify the songbird gene that codes for GnRH1, the hypothalamic decapeptide that stimulates the secretion of gonadotropins by the pituitary gland and, consequently, gonadal development (1, 2, 3). A new study removes this roadblock (4), thus creating new opportunities to address several long-standing questions.

In this study, Stevenson et al. (4) cloned the GNRH1 cDNAs of two songbirds, the European starling and zebra finch, that are extensively used for research in reproductive endocrinology. The nucleotide sequence that is predicted to code for the GnRH1 decapetide was found to present a number of differences between the zebra finch and starling and also between these species and nonsongbird avian species studied to date. Despite these differences, the amino acid structure of GnRH1 was found to be conserved across species examined. Immunoreactive GnRH1-containing neurons in songbirds are located primarily in the preoptic region (5, 6, 7). Confirming this observation, Stevenson et al. found GNRH1 mRNA expression, as determined by RT-PCR and in situ hybridization, to likewise be confined to this area of the brain.
The activity of the reproductive system in many songbirds is regulated primarily by day length (1, 2, 8). In these birds, exposure to sufficiently long days stimulates reproductive development by increasing the production and secretion of GnRH1. Prolonged exposure to these long days, however, desensitizes the GnRH1 system to this stimulus. Birds in this condition are said to be photorefractory and undergo gonadal regression (8, 9, 10). The development of photorefractoriness is a key event in the annual reproductive cycle of seasonally breeding birds, but even though the reproductive consequences of photorefractoriness are well described, the process that initiates is speculative. Recently photorefractory birds generally retain a large pool of releasable GnRH1 whereas brain stores of GnRH1 in deeply photorefractory birds are low (6, 11, 12, 13). This observation led to hypothesize that photorefractoriness develops as a two-step process consisting in decreased secretion and then decreased production of GnRH1 (1).

To test this hypothesis, Stevenson et al. (4) measured the gonad size and preoptic region expression of the GNRH1 gene in male starlings that they transferred from short days to chronically long days until birds became photorefractory. In this experiment, photoinduced changes in GNRH1 gene expression and gonad size followed parallel time courses as starlings became photorefractory. This finding is significant because it suggests that contrary to the current model, an early event associated with photorefractoriness in starlings consists in decreased expression of the GNRH1 gene and therefore presumably also of GnRH1 peptide production.

The identification of the songbird GNRH1 gene will facilitate the use of these organisms to more directly address a number of unresolved issues in avian neuroendocrinology:

Species such as the Japanese quail, Coturnix coturnix japonica, and desert sparrows of the genus Aimophila terminate a reproductive cycle not by becoming absolutely photorefractory, as do starlings but by developing relative photorefractoriness (14, 15, 16). By contrast with absolutely refractory birds, relatively photorefractory birds are thought to retain large hypothalamic stores of GnRH1 that can be released in response to sufficiently long photoperiod or appropriate nonphotic or pharmacological stimulation (17). Does significant production of GnRH1 continue as long as birds remain relatively photorefractory? Is the control of GnRH1 production in relatively photorefractory species fundamentally different from that in absolutely photorefractory species? Studies comparing GNRH1 gene expression in absolutely and relatively photorefractory species should help answer these questions.

As in other photoperiodic vertebrates, the activity of the reproductive system in songbirds is influenced by nonphotoperiodic factors such as water and food availability (18, 19, 20), temperature (21), and social interactions with conspecific and heterospecific birds (22, 23, 24). How the nervous system integrates this influence to fine-tune GnRH1 production and secretion has long been of interest to avian neuroendocrinologists but remains poorly understood. Investigations aimed at measuring the effect of nonphotoperiodic factors on GNRH1 gene expression as well as the time course of these effects will assist us in understanding the influence of nonphotic stimuli on the reproductive system and the neural mechanisms mediating this influence. A comparative approach will be particularly fruitful as the relative sensitivity of the reproductive system to nonphotic cues is likely species specific.

The discovery of the hypothalamic neuropeptide gonadotropin-inhibitory hormone (GnIH) (25) and studies on the physiological actions of this hormone (26, 27, 28) demonstrated that the pituitary gland secretion of gonadotropins in birds is under dual control: stimulatory (GnRH1) and inhibitory (GnIH) (29). In starlings, GnIH fiber terminals contact GnRH1 cell bodies and GnRH1 neurons express GnIH receptors, suggesting that GnIH directly modulates GnRH1 cell function (30). Much remains to be discovered about the mechanisms involved this modulation. Does GnIH influence the production, transport to terminals, and/or secretion of GnRH1? What is the importance of this influence in the control of seasonal functions, in particular photorefractoriness? If GnIH affects GnRH1 production, what molecular pathway mediates this action?

Addressing the above and related questions did until now present almost intractable challenges to endocrinologists studying songbirds. The findings of Stevenson et al. (4) change this situation by offering new and exciting research opportunities that promise to keep songbirds at the forefront of research in vertebrate reproductive endocrinology for the foreseeable future.

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Abbreviation: GnIH, Gonadotropin-inhibitory hormone.


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