

Neural aromatization accelerates the acquisition of spatial memory via an influence on the songbird hippocampus

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Abstract

Circulating estrogens affect the neural circuits that underlie learning and memory in several vertebrates via an influence on the hippocampus. In the songbird hippocampus local estrogen synthesis due to the abundant expression of aromatase may modulate hippocampal function including spatial memory performance. Here, we examined the effect of estradiol, testosterone, and dihydrotestosterone on the structure and function of the songbird hippocampus. Adult male zebra finches were castrated, implanted with one of these steroids or a blank implant, and trained on a spatial memory task. The rate of acquisition and overall performance on this task was recorded by direct observation. The size and density of cells in the hippocampus and its volume were measured. Estradiol-treated birds learned the task more rapidly than any other group. Although testosterone- and blank-implanted birds did learn the task, we found no evidence of learning in dihydrotestosterone-implanted subjects. Cells in the rostral hippocampus were larger in estradiol- and testosterone-treated birds relative to other groups. A corresponding decrease in the density of cells was apparent in estradiol-implanted subjects relative to all other groups. These data suggest that estradiol may accelerate the acquisition of a spatial memory task and increase the size of neurons in the rostral hippocampus. Since testosterone-mediated changes in acquisition and cell size were similar to those of estradiol, but not dihydrotestosterone, we conclude that neural aromatization of testosterone to estrogen is responsible for effects on the structure and function of the songbird hippocampus. © 2004 Elsevier Inc. All rights reserved.

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Introduction

Estrogenic enhancement of memory performance has been reported in several vertebrates including humans (Sherwin, 1996), non-human primates (Bellino and Wise, 2003), and murine rodents (Gibbs, 1998; McEwen, 1994; Woolley et al., 1997). Enhancement of memory performance seems to occur via the potent activational effects of estradiol (E₂) on the hippocampus (HP). More specifically, in rodents, exogenous E₂ increases the number of dendritic spines on HP neurons and the number of synapses onto these dendritic spines (Murphy and Segal, 1996; Woolley and McEwen, 1994; Yankova et al., 2001). Corresponding

changes in HP neuronal function have also been observed including enhancements in synaptic transmission and spatial memory performance (Gibbs, 1998; Woolley et al., 1997). Thus, HP structure and function are sensitive to estrogens in several vertebrates.

In songbirds (order Passeriformes), in addition to peripheral sources, the brain itself synthesizes E₂ due to the abundant expression of aromatase (*estrogen-synthase*) (Schlinger and Arnold, 1991, 1992). Aromatase is especially enriched in the HP, a characteristic well conserved across every songbird species investigated (Fusani et al., 2000, 2001a,b; Metzdorf et al., 1999; Saldanha and Schlinger, 1997; Saldanha et al., 1998, 1999, 2000; Shen et al., 1994, 1995). Notably, HP aromatase is extremely low or undetectable in adult non-songbirds and adult mammals (Roselli and Resko, 1997; Saldanha et al., 1998). Presumably, HP aromatization of testosterone provides high levels of local E₂ available to maintain the integrity and function of HP circuits.

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Songbirds have long been used as excellent models for the study of learning and memory. Although much of this work involves song-learning (Marler, 1997), emerging experimental paradigms have exploited other ecologically relevant behaviors to reveal HP-associated spatial memory for the location of food in black-capped chickadees (*Poecile atricapilla*; Sherry and Vaccarino, 1989), dark-eyed juncos (*Junco hyemalis*; Hampton and Shettleworth, 1996) and zebra finches (Patel et al., 1997), the search for nest-sites in brown-headed cowbirds (*Molothrus ater*; Reboresda et al., 1996), and episodic-like memory in scrub jays (*Aphelocoma coerulescens*; Clayton and Dickinson, 1998; Emery and Clayton, 2001). Indeed, as in other vertebrates, the HP is necessary for spatial memory function in several songbirds (Hampton and Shettleworth, 1996; Patel et al., 1997; Sherry and Vaccarino, 1989), suggesting that mechanisms of HP-dependent memory function may be well conserved across several vertebrate classes.

In the zebra finch (*Taenopygia guttata*), aromatase is expressed at extremely high levels in the HP (Saldanha et al., 1998; Shen et al., 1994, 1995), suggesting that the role of neural E₂ synthesis on brain function may be well studied in these individuals. To test whether steroids such as E₂ play a role in regulating HP structure and function, we determined the effects of E₂, testosterone (T) and the non-aromatizable androgen-dihydrotestosterone (DHT) on: (a) performance on a spatial memory task and (b) HP volume, cell number, and cell size.

Materials and methods

All subjects were housed and treated under the University of California Chancellor's Animal Use Guidelines. Adult male zebra finches (ZFs) were deeply anesthetized (Equithesin) and castrated using previously published protocols (Arnold, 1975b). After removal of the testes, a 10-mm silastic implant containing either estradiol (E₂; Steraloids EO950-000; *N* = 6), testosterone (T; Steraloids A6950-000; *N* = 5), dihydrotestosterone (DHT; Steraloids A2570-000; *N* = 6) or nothing (B; *N* = 7) was dropped into the abdominal cavity. The incisions were closed with Collodion (Mallinckrodt Baker) and subjects allowed to recover for a period of 10 days. During the recovery period, subjects were housed individually under a 14:10 LD cycle. Temperature was maintained at 20°C, and food and water were available ad libitum.

Behavior acquisition of spatial memory

All subjects were trained to perform a spatial memory task before surgery as follows. Birds were housed individually and exposed to the test tray daily. The test tray consisted of seven compartments, all of which were open (no flaps) with the food clearly visible in one compartment. Over successive days, the empty compartments were cov-

ered with flaps beginning with one flap and ending with all six empty compartments covered. Finally, the compartment containing food was also covered and the bird was required to lift off the flaps to find the food.

Following post-surgical recovery, subjects were trained to perform a new spatial memory task, and all behavioral data were collected by an assistant who was blind to the experimental condition (treatment group) of the animal. Importantly, during this phase, the compartment that contained food was different from the training period. Each bird was tested individually in its home cage, once per day. After 2 h of food deprivation, the bird was presented with an experimental tray containing a unique pattern of seven compartments, one of which was filled with seed. Birds were trained to return to the one compartment that contained the seed hidden under one of the seven flaps that covered these compartments. The hidden food was placed in the same location on every trial (Patel et al., 1997). For each trial, we recorded the number of flaps that a bird removed. Each bird was given 5 min to find the food by removing flaps and then allowed to eat for 30 s. If birds search at random, they should lift four flaps on average to find the food, whereas if they use memory to solve the task, they should lift significantly fewer flaps. Memory performance was measured in terms of the number of flaps lifted to find the hidden food across the 20 days and binned into 5-day intervals (see Fig. 1).

Singing behavior was used as an independent measure of the efficacy of steroid implants and castrations. On day 21, all subjects were exposed to stimulus females and the number of song bouts was recorded over a 15-min interval. A song bout was operationally defined as a consecutive series of at least three songs initiated with an introductory series of chirps (see Marler, 1997) and preceded by at least 15 s of no singing.

Anatomy

Following exposure to stimulus females, all subjects were transcardially perfused with 5 ml 0.1 M phosphate buffer (PB) and 30 ml 4% paraformaldehyde (PF; pH = 7.35). At the time of perfusion, the abdominal cavity was opened and the implants visually inspected. Only birds in which the implant was found to yet contain crystalline steroid (except for blank implants) were used in the behavioral and histological analyses.

The brains were removed and post-fixed overnight at 4°C in PF, immersed in 10% sucrose, 20% sucrose, and 25% sucrose (overnight each at 4°C), and gel-embedded in 8% gelatin. The gel blocks were immersed in PF containing 25% sucrose for 48–72 h at 4°C. Coronal sections (50 µm) were cut on a freezing microtome and collected into 0.1 M PB. Every fifth section was mounted onto subbed glass slides, stained with 0.187% thionin, dehydrated, and coverslipped as previously described (Saldanha et al., 2000).

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