Development of the Cerebral Cortex: XI. Sexual Dimorphism in the Brain

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Do sexual differences in the organization of the brain exist, and if so, why? Are they caused by environment or genetics? In fact, the evidence for sexual dimorphism in the brain is compelling. In many animals, distinct differences between sexes in brain morphology have been found that are believed to be responsible for a number of the observed behavioral differences between the sexes.

How do these differences arise and affect behavior? Many result from the differential expression of gonadal steroid hormones during early critical periods of brain development.

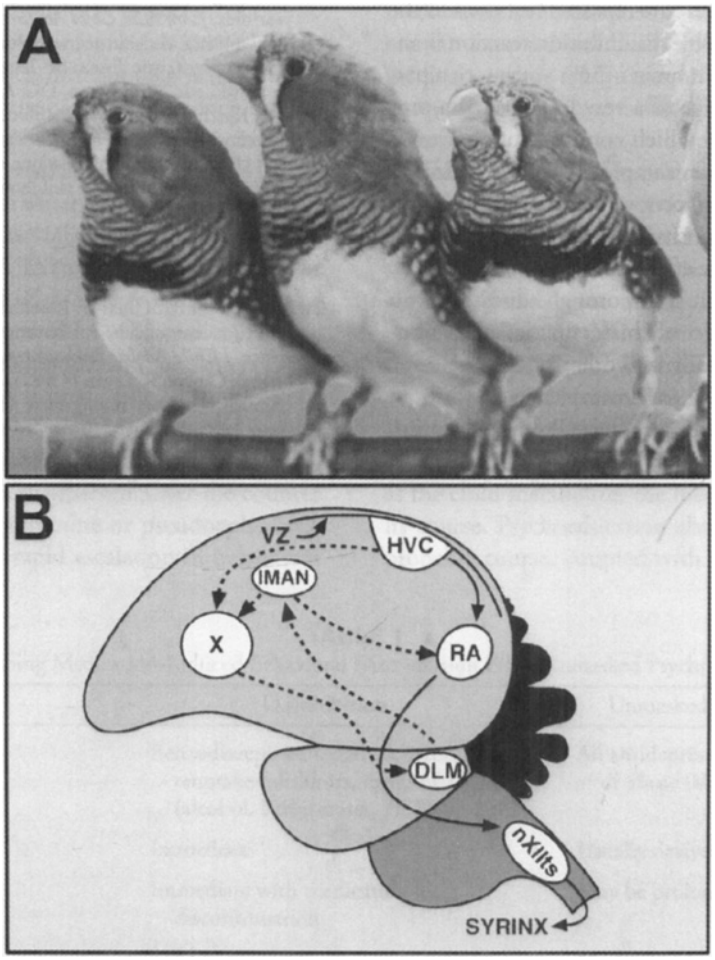

Fig. 1 *A:* Three adult male zebra finches. *B:* Schematic parasagittal drawing of many of the control regions for song production and their connections. Dorsal is up and rostral is to the left. Connections within the efferent pathway for vocal motor control are depicted with *solid black lines*. *Hatched lines* show a pathway that is important for song learning but not song production. DLM = medial portion of dorsolateral nucleus of the thalamus; HVC = high vocal center; LMAN = lateral magnocellular nucleus of the anterior neostriatum; RA = robust nucleus of the archistriatum; VZ = ventricular zone of the lateral ventricle; X = area X; nXIIts = tracheosyringeal portion of the hypoglossal nucleus.

In this column, we review the mechanisms by which these hormones exert their effects.

Testosterone is secreted at much higher concentrations by the testes than by the ovaries. Testosterone and its two primary derivatives, dihydrotestosterone and estradiol, are carried into the brain in the blood. As was reviewed recently, the receptors for neurotransmitters or growth factors lie embedded in the outer plasma membrane and bind their ligands in the extracellular space. In contrast, the classical steroid receptors are found within neurons. Steroids are synthesized from cholesterol and are therefore able to diffuse through the lipid bilayer of the neuronal plasma membrane and bind to their specific receptor.

The hormone-receptor complex then binds to an enhancer sequence of nucleotides within the promoter region of a target gene to modulate gene transcription. Gene expression is thus either up- or down-regulated (enhanced or diminished). The proteins that are synthesized lead to the formation of specific neural circuits within the male brain. The absence of these androgen hormones during critical periods of CNS development leads to the formation of different neural circuits within the female brain.

Perhaps the best studied "simple" system for understanding how steroid hormones orchestrate the development of sexually dimorphic neural circuits is the spinal nucleus of the bulbocavernosus (SNB) in mammals. This is a small population of motor neurons located in the lumbar spinal cord that innervates some of the penile musculature in males and is reduced in size or absent in females. The human homolog is called Onuf's nucleus.

In rats, sex differences in SNB neuron number arise postnatally. Initially, males and females have similar numbers of motor neurons and both possess the presumptive penile musculature. However, the musculature degenerates in females over the first postnatal week as do most, if not all, of the corresponding SNB motor neurons. Sex differences in circulating androgens that occur shortly after birth are thought to be responsible for sex differences in programmed cell death. Early androgen treatment of females is associated with permanent rescue of these motor neurons.

A more complex model for studying sex differences in brain and behavior is the control of birdsong, a learned behavior used to attract mates during the breeding season. The neural circuitry for song production includes cell groups in all major subdivisions of the brain (Fig. 1). Although progress toward understanding the development of sex differences in this system has been much slower than for the SNB, a complex, interconnected system of brain regions such as that for vocal control in birds might ultimately provide a better model for understanding sex differences in complex behaviors across vertebrates, including humans.

Song has intrigued scientists and lay persons alike for centuries, in part because it is often pleasing to the human ear. Young birds learn to sing from their adult companions. This has been demonstrated in three ways. First, birds raised in isolation from members of their own species fail to develop normal song. Second, abnormal song occurs after deafening early in their lives. Third, birds raised in isolation but who are exposed to recordings of song will incorporate many of the song elements into their own vocal repertoire. The fidelity engendered by the vocal memory system in birds can be quite remarkable. Individuals of some species will produce a song with exactly the same acoustic structure over the course of several years, despite the fact that during the many months between successive breeding seasons singing is reduced or absent.

In songbird species such as the zebra finch, only males sing. The regions of the brain that control vocalization are several times larger in male finches than in females. The high vocal center (HVC) and robust nucleus of the archistriatum (RA) of adult male zebra finches are roughly five times larger than in females. This size disparity is due to differences in the number, size, amount of dendritic arbor, and pattern of synaptic connections between the neurons that are present in these regions. Indeed, the largest song control area in the zebra finch, known as area X, cannot even be recognized in females.

The sexual differentiation of vocal control regions in birds occurs after birth. During the first weeks after hatching, the size and number of neurons in HVC and RA are similar in males and females. The sexes diverge shortly thereafter, and females lose many more neurons than do males through differential cell death. Interestingly, exposing a young zebra finch female to testosterone rescues many of the neurons that would normally die.

These findings suggest parallels between the sexual differentiation of vocal control circuits and the SNB. However, there may also be important differences between these systems. Unlike the SNB, the HVC and area X continue to receive new neurons throughout life. Thus, the establishment of sex differences in neuron number within these brain regions may result from hormonal influences on mitotic activity or the migratory routes that neuroblasts take. Indeed, the developmental divergence between the sexes in HVC neuron number can be best characterized as a gradual decrease in cell number in females and an increase in cell number in males. Moreover, the only reported sex difference in cell death within area X is extremely modest compared with the huge dimorphism in the size of this brain region in adulthood. Although cell death most likely participates in the formation of sex differences in all of these regions, other mechanisms may also be involved.

What are the functional consequences of the observed differences in these brain regions? The magnitude of anatomic sexual dimorphism within the song system across species is

related to the degree of behavioral dimorphism in song production. Zebra finches are at one extreme. Species in which males and females engage in complex duets show little or no sex differences in neuron number, cell size, or elaboration of dendritic arbor. As already mentioned, zebra finch females normally do not sing. However, females exposed to testosterone during the early posthatching period develop larger, more male-typical song control regions than normal females and they will sing when given androgens in adulthood.

In some species, this remarkable neural and behavioral plasticity can be induced in adulthood. Adult female canaries exposed to androgens will develop over the course of several weeks a male-like song that is associated with newly formed neurons and growth of HVC. Thus, there is an excellent correlation between the number of vocal control neurons a bird has and its capacity for song production.

Are there any costs to a male for having a large song control system? Adult zebra finches do not show a sex difference in overall brain size, which means that relatively more brain space is committed to vocal control in males than in females. The functional significance of this reverse sexual dimorphism awaits further research. Songbirds provide a valuable model for understanding interactions between hormones, brain, and behavior.

WEB SITES OF INTEREST

http://www.williams.edu/Biology/hwilliams/hwilliams.html
http://www.lifesci.ucla.edu/physci/Faculty/Arnold/index.html
http://www.geocities.com/Athens/2187/mresea.html
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Use of Calcium Channel Blockers and Risk of Suicide: Ecological Findings Confirmed in Population Based Cohort Study.
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Objective: To investigate possible associations between use of cardiovascular drugs and suicide. *Design:* Cross sectional ecological study based on rates of use of eight cardiovascular drug groups by outpatients. A population based cohort study including users of drugs to control hypertension. *Subjects:* The ecological study included 152 of Sweden's 284 municipalities. The cohort study included all inhabitants of one Swedish municipality who during 1988 or 1989 had purchased cardiovascular agents from pharmacies within the municipality. Six hundred and seventeen subjects (18.2%) were classified as users of calcium channel blockers and 2780 (81.8%) as non-users. *Main Outcome Measures:* Partial correlations (least squares method) between rates of use of cardiovascular drugs and age standardized mortality from suicide in Swedish municipalities. Hazard ratios for risk of suicide with adjustments for difference in age and sex in users of calcium channel blockers compared with users of other hypertensive drugs. *Results:* Among the Swedish municipalities the use of each cardiovascular drug group except angiotensin converting enzyme inhibitors correlated significantly and positively with suicide rates. After adjustment for the use of other cardiovascular drug groups, as a substitute for the prevalence of cardiovascular morbidity, only the correlation with calcium channel blockers remained significant ($r = 0.29$, $P < 0.001$). In the cohort study, five users and four non-users of calcium channel blockers committed suicide during the follow up until the end of 1994. The absolute risk associated with use of calcium channel blockers was 1.1 suicides per 1000 person years. The relative risk, adjusted for differences in age and sex, among users versus non-users was 5.4 (95% confidence interval 1.4 to 20.5). *Conclusions:* Use of calcium channel blockers may increase the risk of suicide. **BMJ** 1998;316:741–745