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Review

The genetics of sex differences in brain and behavior

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ABSTRACT

Biological differences between men and women contribute to many sex-specific illnesses and disorders. Historically, it was argued that such differences were largely, if not exclusively, due to gonadal hormone secretions. However, emerging research has shown that some differences are mediated by mechanisms other than the action of these hormone secretions and in particular by products of genes located on the X and Y chromosomes, which we refer to as direct genetic effects. This paper reviews the evidence for direct genetic effects in behavioral and brain sex differences. We highlight the 'four core genotypes' model and sex differences in the midbrain dopaminergic system, specifically focusing on the role of *Sry*. We also discuss novel research being done on unique populations including people attracted to the same sex and people with a cross-gender identity. As science continues to advance our understanding of biological sex differences, a new field is emerging that is aimed at better addressing the needs of both sexes: gender-based biology and medicine. Ultimately, the study of the biological basis for sex differences will improve healthcare for both men and women.

1. Introduction

Men and women are different in many ways. These differences include both biological phenotypes [e.g. 191] and psychological traits [e.g. 200]. Some of these differences are influenced by environmental factors [1,340]. Yet, there are fundamental differences between the sexes that are rooted in biology.

Of particular interest are sex differences that have been identified in the brain. Although the brains of men and women are highly similar, they show consistent differences that have important implications for each sex. That is, brain sex differences uniquely affect biochemical processes, may contribute to the susceptibility to specific diseases, and may influence specific behaviors. Such biological differences should never be used to justify discrimination or sexism. However, we believe that a thorough understanding of these differences can inform researchers and clinicians so that they can better address important issues. Two examples include how genetic sex can lead to differences between the sexes in the etiology and the progression of disease and how differences in neural development may result in differences in cognition and behavior.

In this paper, we will review sex differences in brain and behavior that are not due to the action of hormones secreted by the gonads—which has been the dominant mechanism associated with such differences—but to what we term 'direct genetic effects.' These are effects that arise from the expression of X and Y genes within non-gonadal cells and result in sex differences in the functions of those cells. First, we will highlight some sex differences at the biological level and at the psychological level. Then, we will review the 'classic' view that dominated the field of sex differences—that most sex differences, especially those concerned with reproductive physiology and behavior, were due to the action of hormones produced by the gonads. Next, we will present the emerging view that 'direct genetic effects' play an important role as well. Finally, we will discuss novel approaches to studying sex differences by focusing on unique groups of individuals: people with sex-chromosome variations (e.g., Klinefelter Syndrome and Turner Syndrome), people with genetic mutations in the sexual development pathway, people with an atypical sexual-orientation, and people who experience a cross-gender identity.

2. Biological sex differences

There are many biological differences between males and females that are beyond the obvious differences at a gross, macro level (e.g., height, weight, and external genitalia). Specifically, there are several important physiological differences that have critical implications including the susceptibility to different diseases and the ability to metabolize different medications. In this section we will highlight some sex differences in neuroanatomy and neurochemistry.

2.1. Neuroanatomy

The two sexes have similar but not identical brains. Most brain studies have focused on gross manifestations of these

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Table 1
Selected neuroanatomical sex differences in the rat.

Structure/region	Known roles	Sex difference	Basis of difference
Sexually dimorphic nucleus of the preoptic area (SDN-POA)	The POA is implicated in the regulation of male copulatory behavior [225]. Lesions of the SDN alone slow acquisition of this behavior. Potential human equivalent is INAH-3 [4]	2.6 times larger in males [118]	Perinatal aromatized androgen decreases neuronal apoptotic rates in males [317]
Anteroventral periventricular nucleus (AVPV)	Involved in regulating the luteinizing hormone surge in females [317] and male copulatory behavior [262]	2.2 times larger in females with a higher cell density [45]	Degeneration of cells in this region is greater in males [308] due to prenatal action of androgen
Bed nucleus of stria terminalis (BNST)	Plays a role in the control of male sexual behavior [100], release of gonadotropin [32], and modulation of stress [329,134]	The principal nucleus (BNSTp) is larger in volume in males [85]	The larger volume in males is due to sexually different apoptotic rates caused by testosterone [109]
Corpus callosum	Conducts information between the two halves of the cortex [304]	Larger in neonatal males [351]	Organizational effects of testosterone lead to masculinization while feminization appears to be dependent on estrogens [106,105]
Arcuate nucleus (ARC)	Helps regulate the estrus cycle [203], appetite and body weight [217]	Neurokin-B neurons innervate capillary vessels in the ventromedial ARC in post-pubertal males only [66]	Dihydrotestosterone is responsible for the masculine projection pattern [67]
Amygdala	Strongly associated with emotion, decision-making and Pavlovian conditioning [288]	Adult males have a larger medial nucleus than adult females [221] The posterodorsal aspect of the medial amygdala is 65% larger in males [148]	Treatment of females with estradiol masculinizes this nucleus [221] Activational effects of circulating androgens account for the larger region in males [73]
Cerebral cortex	Connected to a wide range of processes from memory [20] to language [33] to emotional processing [237]	Right posterior cortex is thicker than left but only in males [90]	Gonadal hormones play a role in maintaining the sex difference (ovariectomy masculinizes the cortex of females) [90]
Ventromedial hypothalamic nucleus (VMN)	Involved in the control of lordosis, mounting, and norepinephrine release [102]. High concentrations of steroid receptor mRNA have been observed in the ventrolateral VMN [297]	Females have less synapses in the ventrolateral VMN compared to males [211]	Organizational effects of aromatized testosterone appear to be crucial in establishing the masculine trait [253]
Substantia nigra pars compacta	Made up almost entirely of dopaminergic neurons. Dopamine is involved in control of motor activity [123]	Females have 20% fewer dopaminergic neurons [86]	A genetic component has been demonstrated in mice [60]

Note: This table highlights some prominent sex differences in the rat brain but it is by no means exhaustive. Conflicting evidence concerning the examples reported here (particularly in the SDN-POA) exist, and the interpretation of the data is often more complicated than this summary implies.

differences—namely the size of specific regions or nuclei. Yet, there is mounting evidence of sex differences at a finer level including differences in synaptic patterns [120,66] and neuronal density [117,211,338]. It is beyond the scope of this article to provide a comprehensive review of all known neuoranatomical differences. We have provided notable sex differences in the rat brain in Table 1. There are also excellent resources for those who are interested in delving deeper into this topic [146,98,28].

We have chosen to focus on neuroanatomical differences in the rat because the biological significance and origins of these differences are much clearer than in humans. Neuroanatomical differences in humans are also well-studied although ethical reasons preclude the experimental manipulations that have led to the findings detailed in Table 1. This significantly limits the conclusions that can be drawn from any observations made in humans.

Although these neuroanatomical differences are intriguing, most are limited because the practical or functional significance of these findings are unknown. Discovering the significance of these differences is often difficult, even in rodents. de Vries and Sodersten have eloquently outlined the challenges facing researchers who want to understand the link between sex differences in structure and behavior [82]. A highly relevant case study highlighted in their review concerns the sexually dimorphic nucleus of the preoptic area (SDN-POA). The preoptic area (POA) has been implicated in the regulation of male copulatory behavior [225], but the link (if any) between the sex difference in SDN-POA size and behavior remains elusive. Masculinizing the size of the SDN-POA in female rats does not result in a corresponding masculinization and defeminization of behavior [159]. Instead, the SDN-POA may be related to inhibition of female sexual behaviors [252,141], which might not have been an obvious hypothesis given what was known about the POA previously. As science and technology continue to advance, we will eventually know how to make sense of the mounting evidence of sex differences in the brain. For now, it is reasonable to suspect that such differences may help account for observed sex differences in behavior, neurological diseases, and cognitive abilities.

2.2. Neurochemistry

Males and females exhibit different patterns of transmitting, regulating, and processing biomolecules. Table 2 presents some of the neurochemical sex differences that have been identified. As a specific example, we focus below on the monoaminergic system, which has been implicated in several neurological diseases and mental disorders that differentially affect men and women.

Monoamines are a class of small-molecule neurotransmitters that are involved in the control of a variety of processes including reproduction and sexual behavior [183,170], respiration [112], and stress responses [163]. Monoamines have also been implicated in numerous mental disorders, including ones that differentially affect men and women [283,303]. Likewise, sex differences in the monoaminergic systems in the rat are well-documented. Reisert and Pilgrim provided a comprehensive review of arguments for the genetic bases of these differences [259].

Monoamines are subdivided into two groups—catecholamines and indolamines—based on their molecular structure. The main catecholamines are dopamine (DA), norepinephrine (NE) and epinephrine, which are synthesized from the amino acid tyrosine. Fig. 1 highlights some of the known sex differences of the dopaminergic system. Regulation of dopamine can potentially control the levels of the other two catecholamines as they are derived from dopamine.