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SEX DIFFERENCES IN GENETIC MECHANISMS FOR MAMMALIAN BRAIN AND BEHAVIOR

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SUMMARY

• *There are sex specific genetic mechanisms for mammalian brain and behavior. These are genes that act differently in each sex. They may underlie either similarities or differences in brain and behavior of males andfernales. Some of these genes are autosomal. Others are located on the non-recombining part of the Y chromosome. Genes on this region of the Y chromosome may contribute to sex differences in brain and behavior in three ways. First, a gene may be on the Y chromosome and not on any other chromosome. Thus, it acts only in males. Sex-determining region on the Y chromosome (Sry) is such a gene. Second, there may be different isoforms of proteins coded for by the gene on the Y chromosome and by its homologue located elsewhere in the genome. Such a gene is Smcy which codes for an H-Yantigen. Smcx is its X-chromosomal homologue. Third, there may be different protein levels in males and females for a gene located on the X and Y chromosomes. Zfy and Zfx, for the zinc finger proteins on the Y and on the X, are a pair of such genes. Due to X inactivation in females, one copy of Zfx is expressed in all tissues of female mice, whereas two copies, one of Zfx and one of Zfy, are expressed in many tissues of male mice. (Biomed Rev 1997; 7: 85-90)*

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INTRODUCTION

There are sex specific genetic mechanisms for mammalian brain and behavior. These are genes that have different effects in each sex, and may cause phenotypic similarities or differences between the sexes. Here, I will briefly describe autosomal genes which may be sex specific. The rest of the review will focus on genes of the non-recombining part of the Y chromosome of placental mammals, especially mice, which are obviously sex specific.

AUTOSOMES

• Crossbreeding of inbred strains of mice is being used to identify genes, known as quantitative trait loci (QTL), with effects on complex traits, such as brain and behavior (1,2). The chromosomal positions in cM of genes with effects on trait variation are identified in relation to known markers and genes. These genes may be identified at the molecular level by positional candidates (1) or positional cloning (3). It has been proposed that there are sex specific QTL for hypertension in rats (4), nociception in mice (5), stress-induced analgesia (5), and alcohol preference (6). The *Alcpl* gene on chromosome 2, for example, appears to cause variation in alcohol preference of male but not female mice, whereas the *Alcp2* gene on chromosome 11 appears to cause variation in alcohol preference of female but not male mice. There are many methodological issues that must be considered in firmly establishing findings on QTL (reviewed in 7-9).

Transgenic mice, including knockout mutants, are also being

used to identify genes with effects on complex traits, such as brain and behavior (10). Such genes have already been characterized at the molecular level and their chromosomal position is frequently known. Using knockouts, there appears to be sex specific genes with effects on copulalory, aggressive, and open field behaviors of mice. Knockout mutants for the 5-hydroxylryptamine (5-HT^) receptor (11), monoamine oxidase A (MAO-AX 12), and nitric oxide synthase 1 (NOS-1)(13) affect male but not female copulatory behaviors. The null mutant for Htrlb in males decreases the latency to copulation and increases the frequency of mounting. Also, the null mutants of MAO-A and NOS-1 display abnormal sexual behavior with non-estrous females. Similarly, mutants for cstrogen receptor (ER) (14, 15), MAO-A, NOS-1, and transforming growth factor-a (TGF-a) (16, 17) have differential effects on male and female aggression. The null mutant for NOS-1 decreases latency and increases frequency of attacks in males but not females, and that for MAO-A decrease latency to attack and increase amount of wounding in males but not females. In contrast, the null mutant for ER1 decreases attack duration of male mice paired with male opponents and increases attack duration of female mice paired with female opponents. Similarly, a variant for TGF-a increases aggressive behaviors in males but decreases aggressive behaviors in females. Also, the null mutant for ER decreases open field activity in male but increases it in female mice. There are many methodological issues that must he considered in firmly establishing findings with knockouts and other transgenics (reviewed in 18).

YCHROMOSOME

M Genes on the non-rccombining part of the Y chromosome arc transmitted normally from father to son, and they obviously act and cause variation in males but not females. About 10 genes have been identified on the non-recombining region of the mouse Y chromosome, and about 30 genes have been identified on the non-recombining region of the human Y chromosome (19,20) .Also, there may be an additional 100 to 500 genes on the Y chromosome of mice, humans, and other placental mammals (21). In spite of arguments to the contrary (22), these genes may have an influence not only on variation among male, but also on differences between male and female mammals in brain and behavior.

There arc Y chromosome effects on brain and behavior of male mice. They include effects on hippocampal weight (23), asymmetry in hippocampal size (23), hippocampal mossy fiber distribution (24), whole brain levels of serotonin (25) and dynorphin (26), open Held behavior (27), circadian rhythms (28), coping strategies (29), apomorphinc-induced stereotypy (30), copulatory behaviors (31, 32), aggressive behavior (33-35), and discrimination learning (23). Reciprocal Fls, segregating populations, and congenic strains have been used in these studies. Elsewhere, I have reviewed methodological issues in using these breeding systems to show effects of the non-recombining region of the Y chromosome on traits of male mice (36).

Sex differences have been shown in voles for hippocampal size (37), in rats for hypothalamic and whole brain serotonin levels (38,39), in rodents for regional and whole brain ncuropeptide levels (40), and in mice for open field (11,12), copulatory (41,42) and aggressive behaviors (11,12,43). Since there are Y chromosomal effects in mice on these brain or behavior traits, it is conceivable that genes on the non-recombining region of the Y chromosome by acting in males and not females could contribute at least to these sex differences. A role for the Y chromosome in behavioral sex differences has been suggested (44). A gene, F/p, on the Y chromosome, for example, has been proposed for channel flipping in males and not females. A more serious proposal is made here for three genetic mechanisms involving genes on the Y chromosome of male mice that could account for sex differences in brain and behavior.

A gene on the non-recombining part of the Y chromosome and nowhere else in the genome might have a role in sex differences. There is one such gene on the mammalian Y chromosome. In mice, this is .Sry gene which codes for a high mobility group (HMG) transcription factor (45). This gene is essential for differentiation of the primordial gonad into a testis (46). It is also expressed in brains of marsupials (47), mice (48), and humans (49). The transcript in adult mouse brain is linear and is capable of being translated. Sry protein may bind to five response elements in target genes contributing to activation of their transcription. The Sry protein binds to response elements in the geneFraJ and regulates expression of Fral (50). Fral is a component of activator protein-1 transcription factors which regulate many genes including those coding for neuropeptides (51). Alternatively, Sry may compete with the transcription factors Soxl, 2 or 3 for response elements of target genes and thereby block or attenuate the activation of transcription by Sox 1,2 or 3 (52). Sox 1,2 and 3 are expressed in brain (53). Either of these mechanisms may have a role not only in effects of the non-recombining part of the Y chromosome on brain and behaviors of males, but also of sex differences in brain and behavior.

A gene on the Y chromosome may code for a different isoform of a protein than that coded for by its homologue elsewhere in the genome. An example of this is the gene pair J'mcy andS'mcx in mice. These are transcribed in all tissues including brain. They code for zinc finger transcription factors, and peptides derived from them are minor histocompatibility antigens (54,55). The X- and Y-chromosomal peptides of their antigens differ in five amino acids. There is a second pair of such antigens (UTX and UTY) on the mouse X and Y chromosomes. They differ by three amino acids (56). The genes are transcribed in many tissues including

brain, and their proteins may also be transcription *factors. Rps4y* and *Rps4x* arc another example of genes on the human X and Y chromosomes coding for different isoforms of the same protein (57). Here, there are 19 amino acid differences for a small ribosomal protein. These genes are transcribed in many tissues including brain. Also, this gene is in an area of the human Y implicated in Turner's syndrome. Such differences between males and females in isoforms may contribute to sex differences in brain and behavior.

In placenta! mammals, most but not all genes on one of the X chromosomes of females are inactivated at random in each cell. For these genes, one copy is expressed in all female cells. There are X chromosomal homologues for many Y chromosomal genes of placental mammals (58). Both the X and Y chromosomal genes are expressed in males, or in other words, two copies arc expressed in some, if not all, male cells. An example of ihis is the pair of mouse genes *Zfx* and *Zfy* (59). These are respectively zinc finger on the X and on the *Y.Zfx* is expressed in all cells of males and females, whileZ/y is expressed in some bul not all cells of females. It is not expressed in neurons (60). Another example of this dose difference between males and females is for the *genes Amelx and Amely* (61); for amelogenin of the X and Y, respectively. Amelogenin is a tooth enamel protein. Because of the difference in dose of gene expression in males and females in ameloblasts of tooth buds, males have about 10% more amelogenin then females and may thereby have larger teeth than females (62). There may also be similar dose effect differences for developmental rate or growth factor genes located on the X and Y chromosomes (63-65).

There is recent direct evidence for effects of the Y chromosome on sex differences in behavior. On the C57BL6 background, mice with the Y chromosome from posciavinus are either XY males or XY females (66). The XY females have ovaries or ovatestes. XX females, XY females (ovaries), and XY males on the C57BL6 background have been tested for open field activity, active avoidance, water escape, and Morris maze learning (67). The XX females and XY males differ on each of these behaviors. XY females resemble XX females for open field behavior, active avoidance, and water escape, and XY females resemble XY males for Morris maze learning. These findings arc consistent with the hypothesis that sex differences in open field behavior, active avoidance, and water escape are due to differences in gonadal hormones of males and females, and that the sex difference in Morris maze learning is due to a hormone-independent effect of one or more Y chromosomal genes. It remains to be determined whether other Y chromosomal effects on male brain and behavior and on sex differences in brain and behavior are hormonally dependent or independent. There is at least one gene on the mouse Y chromosome with effects on adult serum levels of testosterone and at least one other gene with effects on target organ sensitivity to testosterone (68).

CONCLUSION

• It has been proposed that there are hormonal and non-hormonal mechanisms for the development of sex differences in mammalian brain and behavior (69,70). Genes, including those of the Y chromosome, are involved in both mechanisms. *Sry,* for example, is involved in determining whether or not the gonad develops as a testis or ovary and thereby the hormonal environment of male or female. These hormones of males and females are involved in sex-specific expression of genes. Some genes described in the section on autosomes may be sex-specific because of effects of sex-specific hormonal environments of males and females. Further research is needed to determine which genes these are. Alternatively, *Sry* may have direct effects on sex differences in brain and behavior which do not involve differences between males and females in hormonal environments. Since Sry is a transcription factor, some of the genes described in the Section on Autosomes may be sex specific because their expression is regulated by Sry in males but not in females. Again, further research is necessitated to define which autosomal genes these are. Such research will contribute to our understanding of the genetic bases for hormonally dependent and independent sex differences in mammalian brain and behavior.

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