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Review

Using mouse models to investigate sex-linked genetic effects on brain, behaviour and vulnerability to neuropsychiatric disorders

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ABSTRACT

Many brain and behavioural phenotypes in humans exhibit some degree of sexual dimorphism. Moreover, there are large and replicable differences in the vulnerability of the two sexes to a wide range of common brain disorders. Ultimately, sex differences in healthy individuals, or in pathological states, must arise as a consequence of the differential complement of sex-linked genes in males and females. These genes may act indirectly (for example through influencing gonadal hormone secretion), or directly, to influence brain development and function. In this review, I discuss how genetically tractable mouse models may be employed to inform our knowledge of the molecular basis of sexual differentiation of the mammalian brain, and how such models may therefore represent a useful tool through which to identify risk factors predisposing to sex-biased neuropsychiatric disorders.

Contents

1. The importance of sex

There is a substantial literature showing that mammalian males and females differ with respect to a number of neurobiological parameters. In humans, sex differences in brain function are evident from the earliest stages of postnatal life [13], right through to old age [108], and across a number of neurobehavioural domains including cognition and emotional function [20]. With regard to cognition, studies have consistently emphasised sex differences in the performance of tasks dependent upon visuospatial function, in perception and in some forms of memory [62]. Modern *in vivo* brain imaging techniques including (functional) magnetic resonance imaging (fMRI) and Diffusion Tensor Imaging (DTI) are now beginning to reveal fine details of sex-specific neuroanatomy and connectivity, to add to the existing data on sex differences in brain structure already gleaned from *post mortem* tissue samples [88]. Many of the sexually dimorphic brain substrates described by these techniques are likely to be neural correlates of the sexually dimorphic behaviours listed above, but it is also possible that in some cases, brain structure differs between the sexes as a compensatory mechanism to ensure that the associated behavioural output is equivalent [20,41]. The overall picture that is emerging is that many sex differences in human neurobiology are consistently observed and are of significant functional relevance [20]; nevertheless, there is still some degree of debate about the verac-

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ity, frequency and magnitude of male–female differences in the normal range [48,72].

In contrast, the existence of sex differences in many pathological conditions is indisputable (even allowing for possible ascertainment biases); indeed, Thomas Insel, Director of the National Institute of Mental Health, was once quoted as saying that 'it's pretty difficult to find any single factor that's more predictive for some of these (neuropsychiatric) disorders than gender' [67]. Sex differences may be observed in the incidence of these disorders, in their age-at-onset and clinical course, in their underlying neurobiology, or in their response to therapy [8,34]. In terms of incidence, males are disproportionately vulnerable to neurodevelopmental disorders such as autism spectrum disorders and Attention Deficit Hyperactivity Disorder (ADHD), whereas females are more vulnerable to later-onset disorders of the affective systems such as unipolar depression, and anxiety-related illnesses [67]. Many of the disorders showing a sex bias in their incidence also show sex biases in their presentation and associated co-morbidities; for example, males diagnosed with ADHD tend to exhibit the hyperactive-impulsive subtype and may present with externalising behaviours such as physical abuse, aggression and criminality whereas females tend to exhibit the inattentive subtype and be at increased risk of developing co-morbid eating and anxiety disorders [11,30]. We know that most, if not all, neuropsychiatric disorders have a substantial (epi)genetic basis, and much work is currently ongoing to identify risk variants [27]. However, whilst common genetic variants that explain just a small fraction of the risk of developing psychiatric disorders receive a disproportionately large amount of attention (and consequently funding), our understanding of how sex, the 'most predictive factor' for some of these disorders, mediates susceptibility remains deficient. Increasing our understanding regarding the molecular basis of sex differences in psychiatric disorders will be pivotal in identifying risk/protective factors and in being able to develop more effective therapies.

2. Sex-linked genetic effects on brain function

Ultimately, sex differences in normal and abnormal brain function must arise as a consequence of the differential sex chromosome complements in male and female cells. In humans, females possess two X chromosomes in each cell, one inherited from either parent. In each cell of the female brain, one of these chromosomes is substantially silenced by the epigenetically mediated process of X-inactivation; which of the two X chromosomes is silenced is initially randomly determined in early embryonic development, but the pattern of X-inactivation is then inherited clonally [6]. In humans, ~15–20% of all X-linked genes escape the process of X-inactivation and remain expressed from both of the X chromosomes [22]. Human males inherit a single X chromosome from their mother and a smaller Y chromosome from their father; in males, X-inactivation does not occur. The X chromosome is enriched for genes important in cognition [146], whilst the Y chromosome also houses several genes expressed to a significant extent in the brain [77]. Therefore, the combined role of these chromosomes in mediating sexually dimorphic neural functions is likely to be important.

There are three general genetic mechanisms via which may give rise to sexually dimorphic gene expression patterns, and hence sexually dimorphic brain phenotypes: expression of Y-linked genes, X-linked gene dosage, and X-linked genomic imprinting [34]. In the first mechanism, given that only males possess a Y chromosome, Y-linked genes can only be expressed in this sex. In the second mechanism, genes which escape the process of X-inactivation may theoretically be more highly expressed in female than male brain cells given that females possess two expressed alleles compared to the male's one. Importantly, due to incomplete escape on the inactivated chromosome, and possible mediating hormonal factors, it is not necessarily the case that if a gene 'escapes' from X-inactivation it will be expressed significantly more highly in female than male cells. Therefore, the ability of the 'escapees' defined by Carrel and Willard [22] to influence sexually dimorphic traits may be somewhat attenuated. In the third mechanism, X-linked 'imprinted genes' (i.e. genes which are monoallelically expressed in a parent-of-origin dependent manner) may exhibit female-limited expression if they are solely expressed from the paternally inherited X chromosome (specific to females), or male-biased expression if they are expressed predominantly from the maternally inherited X chromosome (common to both sexes), and are subject to X-inactivation [33,36]. Imprinted genes are currently a hot topic in developmental neurobiology [140], and are likely to influence the aetiology of a wide range of behavioural endophenotypes and psychiatric disorders [78]; this class of genes is discussed further in Section 7. Here, it should be made clear that whilst many X-linked genes may be involved in, or be critical to, the expression of particular traits, their expression may not necessarily induce sex-specific phenotypes.

The three distinct genetic mechanisms outlined above may act to influence brain function directly (i.e. the sex-linked genes encode proteins which act within the brain in some capacity) or indirectly (i.e. the sex-linked genes encode proteins which influence the development of some other body tissue such as the gonads or the adrenal glands, which subsequently influence brain development and/or function via systemic compounds such as hormones).

The importance of the mechanisms listed above to brain and behavioural function (whether direct or indirect) is illustrated by the functional consequences associated with their dysregulation. Case studies of individuals with Y-linked chromosomal abnormalities (deletions or duplications spanning multiple genes) have suggested that they may exhibit a number of psychological abnormalities and propensity to a variety of mental disorders [92,97,100,101,106,145].

Individuals with abnormal dosage of X-linked genes as a consequence of reduced or increased numbers of X chromosomes also commonly show behavioural anomalies. Females with the developmental disorder Turner syndrome (TS), most frequently caused by complete loss of one X chromosome (45,X, X-monosomy), exhibit a subtle constellation of psychological problems including attention deficits (and heightened vulnerability to ADHD [120]), impairments in visuospatial skills [102], inability to recognise emotion in faces [79], and anxiety in certain situations [125]. It has also been suggested that subjects with Turner syndrome may be significantly over-represented in samples of females with schizophrenia [109,115], although the data are not consistent [96]. The behavioural abnormalities seen in individuals with Turner syndrome may be partially explained by altered systemic hormone levels, notably reduced estrogen and androgen levels (as a consequence of ovarian dysfunction) and reduced growth hormone levels [58]. Indeed, there is limited evidence that estrogen, androgen and growth hormone replacement therapies may alleviate TS-associated cognitive deficits to some extent [116–118].

The severity of some behavioural and neurological phenotypes in TS may depend upon whether the remaining intact X chromosome is of paternal ($45,X^{P}$, ~30% of 45,X cases) or maternal ($45,X^{M}$, ~70% of 45,X cases) origin [47,63,84,99,121]; such parent-of-origin sensitive phenotypes may theoretically be modulated by the products of one or more X-linked imprinted genes.

Subjects with X-polysomy, i.e. possessing more than the usual complement of X chromosomes (of which Klinefelter's syndrome 47,XXY is the most common), may present with developmental delay, language-based learning disabilities, executive dysfunction (including attention) and socio-emotional difficulties [53,131]; moreover, subjects with Klinefelter's syndrome display increased