Review

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Etiologies underlying sex bias in autism spectrum disorder: a narrative review of preclinical rodent models

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Neurodevelopmental disorders, which emerge early in development, include a range of neurological phenotypes and exhibit marked differences in prevalence between sexes. A male predominance is particularly pronounced in autism spectrum disorder (ASD). Although the precise cause of ASD is still unknown, certain genetic variations and environmental influences have been implicated as risk factors. Preclinical ASD models have been instrumental in shedding light on the mechanisms behind the sexual dimorphism observed in this disorder. In this review, we explore the potential processes contributing to sex bias by examining both intrinsic differences in neuronal mechanisms and the influence of external factors. We organize these mechanisms into six categories: 1) sexually dimorphic phenotypes in mice with mutations in ASD-associated genes related to synaptic dysfunction; 2) sex-specific microglial activity, which may disrupt neural circuit development by excessively pruning synapses during critical periods; 3) sex steroid hormones, such as testosterone and allopregnanolone, that differentially influence brain structure and function; 4) escape from X chromosome inactivation of the O-linked-N-acetylglucosamine transferase gene in the placenta; 5) sexually dimorphic activation of the integrated stress response pathway following maternal immune activation; and 6) immunological responses that are differentially regulated by sex. Understanding these mechanisms is essential for deciphering the underlying causes of ASD and may offer insights into other disorders with notable sex disparities.

Introduction

Background

Neurodevelopmental disorders (NDDs) are a heterogenous group of conditions that manifest during the developmental period and are characterized by impairments in various aspects of neurological functioning [1]. As defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, NDDs include autism spectrum disorder (ASD), intellectual disability/developmental delay, attention-deficit/hyperactivity disorder, motor and tic disorders, and specific language disorders. These conditions can lead to a range of developmental deficits, from specific challenges in learning or executive function management to more extensive impairments in social skills or intellectual abilities [2]. This review is primarily focused on ASD, a NDD marked by deficits in social interaction and engagement in repetitive and stereotyped behaviors [2].

The prevalence, age of onset, pathophysiology, and symptomatology of many NDDs vary substantially by sex. A pronounced male bias is evident in ASD, with a male-to-female prevalence of approximately four to one [3,4]. The potential underdiagnosis of females with ASD has raised concerns, suggesting the need for distinct diagnostic criteria in their assessment [5,6]. Even apart from variations in diagnostic practices, a sex bias persists in the prevalence of ASD, with a male-to-female ratio ranging from at least 2:1 to 3:1. This highlights the critical need to explore the biological basis of sexual dimorphism, which may be key to understanding the processes underlying ASD pathogenesis [7].

Here, we explore the potential mechanisms contributing to the sex-biased prevalence disparity in ASD using various preclinical models (Table 1). While preclinical rodent models of ASD cannot fully replicate the spectrum of human ASD phenotypes [8], potentially due to differences in brain structures and developmental trajectories [9], they remain invaluable for gaining mechanistic

Table 1. Potential contributing mechanisms underlying the sex-biased prevalence of ASD as demonstrated in preclinical rodent models

Potential contributing mechanisms	Preclinical models showing sexually dimorphic ASD-like phenotypes	Suggested mechanism(s)	References
Synaptic dysfunction	*Shank3* KO	Reduced levels of mGluR5 in male mice	[27]
	Chd8$^{+/N2373K}$	Sexually dimorphic changes in neuronal activity, synaptic transmission, and transcriptomic profiles	[40]
	Fmr1 KO	Sexually dimorphic upregulation of ASD risk genes (male↑: *Ctnnb1*[a] and *Grin1*[a], female↑: *Homer1*[a], *Ptgs2* [a], *Drd1*[a], *Pik3ca*[b], and *Csnk1g1*[b])	[44]
Microglial abnormalities	*Cntnap2* KO	Activated morphology and phagocytosis of synaptic structures in male microglia	[58]
	DEP/MS	Hyper-ramified phenotype in male microglia	[63]
Hormones	VPA-induced ASD mouse model	Lower levels of TH expression in the AVPV of male mice	[70]
	Placenta-specific *Akr1c14* KO	Male mouse-specific abnormalities in cerebellar white matter	[75]
Escape from X chromosome inactivation	Prenatal stress model	Placental OGT expression levels are twice as high for female fetuses as for male fetuses; this results in sexually distinct gene expression in trophoblasts through epigenetic modulation by histone methylation	[79,80]
Integrated stress response pathway	MIA (Poly[I:C])	Hyperactivation of the ISR pathway in male MIA offspring, resulting in reduced nascent protein synthesis in the brain	[85]
Immune pathways	Prenatal GBS infection	Heightened levels of pro-inflammatory cytokines and chemokines such as IL-1β and CINC-1/CXCL1 in male fetuses	[98]
	MIA (LPS)	Male MIA offspring exhibit heightened cortical hypoxia, reduced mitosis of radial glial cells, disrupted E/I balance within the brain, severe placental necrosis, elevated inflammation, and reduced placental growth	[99]
	MIA (two-hit model)	The anti-inflammatory cytokines IL-10 and TGF-β1 are decreased in male offspring but increased in female mice	[100]

↑: upregulated, [a]: high-confidence risk genes for ASD, [b]: suggestive risk genes for ASD.

ASD, autism spectrum disorder; *Shank3*, SH3 and multiple ankyrin repeat domains 3; KO, knockout; mGluR5, metabotropic glutamate receptor 5; *Chd8*, chromodomain helicase DNA-binding protein 8; *Fmr1*, fragile X mental retardation 1; *Ctnnb1*, catenin beta 1; *Grin1*, glutamate ionotropic receptor NMDA type subunit 1; *Homer1*, homer scaffold protein 1; *Ptgs2*, prostaglandin-endoperoxide synthase 2; *Drd1*, dopamine receptor D1; *Pik3ca*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *Csnk1g1*, casein kinase 1 gamma 1; *Cntnap*2, contactin-associated protein 2; DEP/MS, diesel exhaust particles and maternal stress; VPA, valproic acid; TH, tyrosine hydroxylase; AVPV, anteroventral periventricular nucleus; *Akr1c14*, aldo-keto reductase family 1 member C4; OGT, O-linked-N-acetylglucosamine transferase; MIA, maternal immune activation; poly(I:C), polyinosinic:polycytidylic acid; ISR, integrated stress response; GBS, Group B *Streptococcus*; IL-1β, interleukin 1 beta; CINC-1/CXCL1, cytokine-induced neutrophil chemoattractant-1; LPS, lipopolysaccharide; E/I, excitation/inhibition; IL-10, interleukin 10; TGF-β1, transforming growth factor beta 1.

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insights into the pathogenesis of ASD and for exploring potential therapeutic strategies [10,11].

Objectives

This review aims to elucidate the potential contributing mechanisms underlying the sex-biased prevalence of ASD as demonstrated in preclinical rodent models. These include synaptic dysfunction, microglial abnormalities, the influence of sex hormones, escape from X chromosome inactivation, the integrated stress response (ISR) pathway, and immune pathways.

Methods

Ethics statement

The present study is based on a review of the literature; consequently, neither approval from an institutional review board nor the acquisition of informed consent was necessary.

Study design

This study is a narrative review.

Literature search: information sources and search strategies

We searched the PubMed database for articles published from 1990 up to April 2024. Only articles published in English were included.

Results

This review encompasses a total of 104 articles. A list of articles pertaining to each topic is available in the references.

Synaptic dysfunction

Previous studies have reported that those with ASD exhibit different brain connectivity patterns compared to typically developing individuals [12]. Patterns of widespread cortical underconnectivity, local overconnectivity, or a combination of these suggest that disrupted brain connectivity may represent a potential neural signature of ASD [13]. Brain connectivity is largely determined by the characteristics of neurons and synapses, with synapses being highly specialized, asymmetric cell-to-cell junctions that constitute the fundamental units of brain communication [14].

According to the Simons Foundation Autism Research Initiative (SFARI) gene database, hundreds of genes have been identified as being associated with ASD [15–18]. Among these, genes such as those of the SH3 and multiple ankyrin repeat domains (*SHANK*) family, fragile X mental retardation 1 (*FMR1*), and chromodomain helicase DNA-binding protein 8 (*CHD8*) are linked to common cellular pathways that converge at synapses [19–21]. This convergence suggests that synaptic dysfunction may contribute to the development of ASD, potentially leading to functional and cognitive impairments [14].

SHANK, also known as ProSAP, is a family of postsynaptic proteins found at glutamatergic synapses and includes three major isoforms: SHANK1, SHANK2, and SHANK3. These proteins act as master scaffolding proteins at excitatory synapses [22,23]. They interact with over 30 synaptic proteins across multiple domains and are critical for synaptic formation, glutamate receptor trafficking, and neuronal signaling [24]. Genetic screenings have identified mutations, rare variants,

or disruptions of the *SHANK3* gene in patients with ASD [22]. Mice with a genetic disruption of *Shank3* display compulsive/repetitive behaviors and social interaction deficits, which reflect clinical features of ASD [25]. Studies using *Shank3* knockout (KO) mouse models have reported sexually dimorphic phenotypes [26,27]. Matas et al. found that male *Shank3* KO mice with a mutation in the C-terminal regions (exons 21–22) [28] exhibit more pronounced gait deficits than their female siblings [27]. Further research into cerebellar glutamate levels and postsynaptic receptors showed that metabotropic glutamate receptor 5 levels were reduced only in male *Shank3* KO mice, suggesting a potential cause for the varied behavioral outcomes [27].

CHD8, a chromatin remodeling factor, is essential for regulating the transcription of a wide variety of genes [29,30], including approximately 1,000 ASD risk genes identified in the SFARI gene database [30]. Mice with homozygous deletions of *Chd8* die early in embryonic development [31], while those with heterozygous mutations or gene knockdown display a range of ASD-like phenotypes [32–36]. These include impaired social interaction, repetitive behaviors, and cognitive impairments, resembling characteristics of individuals with *CHD8* mutations [20,30,37–39]. Jung et al. found that a heterozygous mutation in *Chd8*, specifically the substitution of asparagine with lysine at position 2373—the first mutation identified as an ASD risk factor in human *CHD8*—results in sexually dimorphic effects that range from transcriptional to behavioral changes in mice [40]. Male $Chd8^{+/N2373K}$ mice exhibited various abnormal behaviors at the pup, juvenile, and adult stages, such as increased ultrasonic vocalizations when seeking their mother, heightened attachment upon reunion with their mother, and increased self-grooming when isolated. In contrast, their female counterparts did not exhibit these behaviors. This behavioral disparity is thought to be associated with sexual dimorphism in neuronal activity, synaptic transmission, and transcriptomic profiles.

The *FMR1* gene encodes the fragile X mental retardation protein (FMRP), which acts as a messenger RNA-binding translational suppressor. It also modulates activity-dependent calcium signaling during critical developmental periods [41]. In mice, FMRP is most abundantly expressed in the hippocampus and cerebral cortex, with peak levels occurring between 2 to 4 weeks postnatally—a crucial time frame for synaptic development and maturation [42]. A deficiency in FMRP results in abnormal synaptic plasticity and structural remodeling [43]. Notably, male *Fmr1* KO mice exhibit more severe anxiety, deficiencies in social preference, and repetitive behaviors than their female counterparts [44]. Differential gene expression analysis of the hippocampus in wild-type (WT) versus *Fmr1* KO mice revealed that in male *Fmr1* KO mice, *Ctnnb1* and *Grin1*—genes considered high-confidence risk factors for ASD—are highly upregulated. In contrast, female *Fmr1* KO mice exhibited upregulation of genes such as *Homer1*, *Ptgs2*, and *Drd1*, which are strong ASD risk gene candidates, as well as *Pik3ca* and *Csnk1g1*, which provide suggestive evidence of risk for ASD. These findings suggest that the loss of FMRP leads to sexually dimorphic phenotypes, potentially due to different patterns of gene expression regulation resulting from the absence of FMR1.

The collective evidence from these reports suggests that synaptic dysfunction and disrupted connectivity could be responsible for sex-specific functional and cognitive impairments observed in ASD [45].

Microglial abnormalities

The balance between excitation and inhibition (E/I) in neural circuits is critical for maintaining brain homeostasis [46]. Disruption of this E/I balance has been implicated as a potential cause of behavioral phenotypes associated with ASD [47]. Microglia, the phagocytic cells that reside

in the brain from the developmental period, engulf the synaptic materials, thus pruning synapses and supporting synaptic maturation. [48]. When microglial function is compromised, improper synaptic pruning can disrupt the E/I balance and potentially contribute to the pathogenesis of ASD [49]. Notably, microglia exhibit sexually dimorphic transcriptional and translational profiles [50]. Furthermore, the morphology and number of microglia in the developing rat brain differ between male and female rats [51]. During the early postnatal period, male rats have significantly higher numbers of microglia compared to female rats. These sex-based differences in microglial numbers appear to be functionally related to sex-specific behaviors [52].

The contactin-associated protein 2 (*CNTNAP2*) gene encodes the CASPR2 protein, which is a neurexin-related synaptic cell adhesion molecule. A study utilizing high-density single nucleotide polymorphisms identified *CNTNAP2* as a strong candidate gene implicated in the etiology of ASD [53]. Subsequent loss-of-function studies in *Cntnap2* KO mice demonstrated that the absence of *Cntnap2* leads to a decrease in dendritic spine density [54], disruptions in synaptic function [55], imbalances in E/I signaling, and impaired neural oscillations [56]. These *Cntnap2* KO mice also display core ASD-like behavioral phenotypes, including impairments in sociability and repetitive behaviors [57]. Dawson et al. found that male *Cntnap2* KO mice exhibited pronounced social deficits, whereas their female counterparts did not. Further investigation into the anterior cingulate cortex—a region critical for social behavior regulation through its connections with other intracortical and subcortical areas—revealed a more activated morphology and increased phagocytosis of synaptic structures in male KO mice compared to WT mice, a distinction not observed in female KO versus WT mice [58].

In addition to genetic models, differences in microglial morphology and function have been observed in preclinical models that incorporate environmental risk factors. High levels of air pollution, particularly during development [59,60], and maternal stress (MS) during gestation [61,62] have been linked to an increased risk of ASD. Smith et al. investigated the combined effects of these two risk factors and found that prenatal exposure to air pollution—specifically diesel exhaust particles (DEP)—along with MS in mice led to sociability deficits exclusively in male offspring [63]. These behavioral impairments were paralleled by alterations in microglial morphology and gene expression, with DEP/MS exposure resulting in a hyper-ramified microglial phenotype in male but not female animals.

The collective evidence from these reports suggests that sexually dimorphic microglial activity could play a role in the etiology of ASD. This activity may disrupt the development of neural circuits responsible for social behavior by excessively pruning synapses during a critical period of development [49].

Hormones

Sex steroid hormones are known to contribute to sex differences in neural activity and behaviors in mammals through their interactions with specific nuclear hormone receptors [64]. Testosterone plays a crucial role during prenatal development in shaping sex differences, influencing brain structure, neurotransmitter and receptor levels, neurogenesis, immune responses, neuropeptide signaling, and cellular processes such as apoptosis, migration, and differentiation [65]. Clinical reports have correlated high levels of testosterone with autistic behavior [66,67], and this association is supported by Erdogan et al., who showed that prenatal testosterone exposure led to ASD-like behaviors in the offspring of Wistar rats [68]. Both male and female rats exposed to testosterone exhibited reduced interaction times with a stranger rat during the three-chamber sociability and social novelty test, indicating a decrease in social

interaction and a phenotype with characteristics resembling ASD. In line with these findings, studies on the valproic acid (VPA)-induced ASD mouse model, which is based on a medication known to increase the risk of ASD in humans [69], have shown that elevated plasma testosterone levels resulting from VPA treatment led to significantly lower levels of tyrosine hydroxylase (TH) expression in the anteroventral periventricular nucleus of male mice. In contrast, TH levels in female mice were unaffected [70].

Allopregnanolone (ALLO), a 3α, 5α progesterone metabolite [71], is a key GABAergic neurosteroid [72,73]. Reduced ALLO levels are correlated with a greater severity of restricted and repetitive behaviors [74]. Penn and colleagues have shown that ALLO plays a vital role as a placental hormone in shaping the fetal brain, leading to sexually dimorphic behavioral outcomes [75]. Specifically, a deficiency of placental ALLO in mice resulted in male-specific abnormalities in cerebellar white matter and core ASD symptoms, such as diminished social preference and increased repetitive behaviors. Notably, this study observed sex-linked dysregulation of myelin proteins in the cerebellar vermis of preterm infants, which aligns with human data.

These results highlight the influence of hormones in molding the early brain environment, potentially leading to sexually dimorphic behavioral outcomes.

Escape from X chromosome inactivation

In a mouse model of early prenatal stress, male offspring exposed to MS during gestation exhibited certain NDD phenotypes [76,77]. The placenta plays a critical role during pregnancy, acting as a mediator in response to disturbances within the intrauterine environment [78]. MS leads to sexually dimorphic changes in the placental expression of O-linked-N-acetylglucosamine transferase (OGT), an X-linked gene essential for the regulation of proteins involved in chromatin remodeling [79]. Notably, OGT escapes X chromosome inactivation in the placenta, resulting in placental levels that are approximately twice as high in female animals than in male animals. Crucially, this finding also translates to humans: levels of both OGT and its biochemical marker, O-GlcNAcylation, have been found to be considerably lower for male fetuses and are further reduced by prenatal stress [79]. Nugent et al. demonstrated that OGT levels establish a sex-specific gene expression pattern in trophoblasts through regulation of a canonical histone repressive mark, H3K27me3 [80]. Higher placental levels of H3K27me3 for female offspring provided a protective effect against the altered hypothalamic programming associated with prenatal stress exposure. Consequently, lower levels of OGT may predispose male offspring to a higher risk of ASD. Future studies should explore the molecular mechanisms underlying this increased male susceptibility.

Integrated stress response pathway

Maternal immune activation (MIA) during pregnancy is linked to a heightened risk of ASD in offspring [81]. This phenomenon has been extensively investigated using a rodent MIA model. In this model, pregnant mice received intraperitoneal injections of polyinosinic:polycytidylic acid (poly[I:C]), a synthetic analog of double-stranded RNA that simulates viral infection. The offspring exhibited significant neurodevelopmental impairments, including diminished social interaction and increased repetitive behaviors [82–84]. Kalish et al. found that MIA exerts a sexually dimorphic effect in utero, leading to different behavioral outcomes. Male offspring exhibited MIA-induced behavioral abnormalities, whereas female offspring did not [85]. Notably, when gene expression was examined at the single-cell level, changes in the fetal cortex were observed to be sexually dimorphic. In male fetuses, these changes were

predominantly characterized by reduced gene expression related to protein translation, followed by an overactive ISR pathway. In eukaryotic cells, the ISR signaling pathway regulates protein synthesis in response to various stresses, both physiological and pathological, to restore cellular homeostasis [86]. Dysregulation of protein synthesis has been implicated in ASD-related traits and other neurological disorders [87–89]. Male-specific activation of the ISR is dependent on the maternal induction of interleukin (IL)-17A following MIA, which has been shown to be necessary for the development of MIA-induced ASD-like behaviors in mouse offspring [83]. The genetic and pharmacological inhibition of ISR pathway hyperactivation was sufficient to protect male offspring from MIA-induced behavioral abnormalities. This study offers valuable insights into potential preventative strategies for ASD-like phenotypes that may result from prenatal immune activation.

Immune pathways

Preterm delivery is associated with a higher likelihood of ASD in children compared to those born at full term [90–93]. Chorioamnionitis, caused by Group B *Streptococcus* (GBS; *Streptococcus agalactiae*), is one of the most common maternal infections and accounts for 40% to 70% of preterm births [94–96]. This condition typically involves an inflammatory intrauterine environment, even in the absence of bacterial translocation from mother to fetus [97]. Allard et al. demonstrated that prenatal infection with live GBS in rats resulted in social impairments in male but not in female offspring [98]. A prominent inflammatory state was noted in male animals, with higher levels of the pro-inflammatory cytokine IL-1β and the cytokine-induced neutrophil chemoattractant-1 (CINC-1/CXCL1), compared to female rats. These findings suggest that sex-specific inflammatory profiles may contribute to the observed sexually dimorphic behavioral outcomes [98].

Consistent with this notion, in a model of MIA induced by lipopolysaccharide (LPS), a toll-like receptor 4 agonist, Braun et al. investigated sex-specific pro-inflammatory responses in both the placenta and fetus, as well as their effects on behavioral outcomes. Male offspring of mothers exposed to LPS exhibited behavioral abnormalities in social interaction and learning, as well as increased repetitive behavior, whereas female offspring were unaffected [99]. Male MIA offspring showed increased cortical hypoxia, decreased mitosis of radial glial cells, and disrupted E/I balance in the brain. Additionally, severe placental necrosis, heightened inflammation, and reduced placental growth were specifically observed in male mice affected by MIA, suggesting that unique sex-specific placental characteristics may make male offspring more susceptible to intrauterine disturbances.

Carlezon Jr et al. demonstrated sex-specific behavioral effects and immune responses in the brain using a combined rodent "two-hit" immune activation model. This model involved treatment with poly (I:C) to induce MIA and the administration of LPS to produce postnatal immune activation [100]. Exposure to early-life immune activation (EIA) was shown to lead to reduced social interaction and increased repetitive behaviors in male animals, while female rodents displayed no significant changes. Molecular studies indicated that EIA resulted in pronounced sex-specific alterations in the expression of inflammation-related genes in the brain. Both male and female rodents exposed to EIA exhibited elevated levels of pro-inflammatory factors in the brain, such as tumor necrosis factor alpha, inducible nitric oxide synthase, IL-6, and IL-1β. Conversely, the expression of anti-inflammatory factors like IL-10 and transforming growth factor beta 1 was reduced in male mice but elevated in female animals [100].

The collective findings of these studies suggest that sexually dimorphic inflammatory

responses could potentially contribute to the sex-specific effects of MS on the neurobehavioral outcomes of offspring.

Discussion

Implication and suggestion

In this review, we have comprehensively examined the potential mechanisms by which genetic variants and environmental factors contribute to sex differences, as demonstrated by preclinical models. Our analysis encompassed both intrinsic differences in the brain, such as synaptic connectivity and microglial activity, and the potential influence of extrinsic factors, including sex hormones and the placenta. These elements may either increase male susceptibility or bolster female resilience. Notably, beyond the intrinsic factors of the brain, the hormonal profile, epigenetic landscape, and immune pathways associated with the placenta have been implicated in contributing to sexually dimorphic outcomes in mouse models exhibiting ASD-like behaviors. This indicates that a deeper understanding of the placenta as a temporary but dynamic interface during prenatal development could provide valuable insights into the sex biases observed in NDDs.

Although preclinical mouse models of ASD have important limitations, such as their inability to engage neural circuitry comparable to that observed in humans or to recapitulate all human ASD phenotypes [8], they remain valuable tools for gaining mechanistic insights into ASD pathogenesis and for developing potential therapeutic approaches [10,11]. Further investigation is imperative to unravel the mechanistic basis of sexual dimorphism in ASD, as well as in other NDDs. For example, utilizing large-scale transcriptomics from postmortem brain studies [101], generating a single-cell atlas [102], and conducting multi-omic profiling of somatic mutations [103] in brains exhibiting ASD could help uncover sex-specific changes in genes or pathways during early neurodevelopment. Given that ASD is a developmental disorder, it is crucial to conduct further longitudinal investigations to understand how risk factors evolve across the developmental trajectory. For instance, a longitudinal cohort study of children with developmental disabilities suggested that *de novo* protein-truncating variants were correlated with clinical characteristics [104].

Conclusion

Overall, understanding sex-specific mechanisms is pivotal for comprehending the fundamental causes of ASD and may illuminate the pathologies of other diseases characterized by prominent sex biases.

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