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Review article

Genes and sex hormones interaction in neurodevelopmental disorders

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ABSTRACT

The prevalence, age of onset and symptomatology of many neurodevelopmental disorders strongly differ between genders. This review examines sex biases in human neurodevelopmental disorders and in validated animal models. A focus is made on disorders of well-established genetic origin, such as Rett syndrome, CDKL5-associated disorders, Fragile X and Down syndrome. Autism is also addressed, given its paradigmatic role as a sex-biased neurodevelopmental disorder. Reviewed literature confirms that a complex interaction between genetic factors and sex hormones may underlie the differential susceptibility of genders and may impact the severity of symptoms in most of the analyzed neurodevelopmental disorders. Even though further studies addressing the advantages and disadvantages conferred by biological sex in this class of disorders are needed to disentangle the underlying mechanisms, present findings suggest that modulation of sex steroid-related pathways may represent an innovative approach for these diseases. Much effort is now expected to unravel the potential therapeutic efficacy of drugs targeting sex hormones-related signaling pathways in neurodevelopmental disorders of well-established genetic origin.

Contents

1. Introduction

Neurodevelopmental disorders (NDDs) represent a wide, clinically heterogeneous group of psychiatric illnesses, caused by aberrant development of the central nervous system. Affected domains include motor function, cognitive abilities, language and affective states. Among most common NDDs, there are autism spectrum disorders, social communication disorders, syndromic and

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non-syndromic intellectual disabilities and attention deficit hyperactivity disorder (APA, 2013).

The prevalence, age of onset, pathophysiology, and symptomatology of many neurodevelopmental disorders strongly differ between genders. The increased vulnerability of males to mutations of X-linked genes is an obvious source of sex differences in diseases (Arnold, 2004). However, it seems apparent that sex dimorphism within this class of neuropsychiatric disorders extends beyond the obvious X-linked pathologies (Baron-Cohen et al., 2011 and Section 3.1). Marked sex differences in terms of incidence and clinical symptoms are in fact evident in disorders of multi-factorial origin characterized by abnormal neurodevelopment, such as schizophrenia and autism (Hill et al., 2004; Kokras and Dalla, 2014; Mottron et al., 2015), thus suggesting that steroid hormones of gonadal origin and neurosteroids can either mask/unmask an underlying vulnerability for behavioral disorders or ameliorate/aggravate the severity of related symptoms (Keller and Ruta, 2010; Knickmeyer and Baron-Cohen, 2006). A better understanding of the mechanisms underlying risk and resilience to disease between the sexes may be of fundamental importance to identify innovative therapeutic targets and pharmacological approaches for these diseases. In this line, promising results are emerging on the potential use of sex steroid hormones and selective estrogen receptor modulators as adjunctive treatments for some of these disorders (Huerta-Ramos et al., 2014; Kulkarni et al., 2014; Weickert et al., 2015). For preclinical research in this framework, see (Biamonte et al., 2009; Macri et al., 2010).

2. Genes and sex hormones interaction in sexually dimorphic brain development

Nowadays it is generally agreed that the brain is a sexually dimorphic organ that can be shaped by sex-specific selection pressures. The classic view of sex dimorphism of the brain postulates that sex-specific differences specifically arise from differential development of the gonads and differential exposure to gonadally-secreted steroid hormones (Miller, 1988; Mottron et al., 2015; Robel and Baulieu, 1994). Once produced, these gonad-derived hormones are released into the systemic circulation to exert their biological activity in a wide variety of reproductive and non-reproductive tissues, including the central nervous system. In particular, in rodent brains, the dominant driver of most sex differences is estradiol, which is locally produced by the portion of circulating testosterone which gains access to the brain (Wu et al., 2009). See Fig. 1 for an overview of the developmental expression of the major hormone synthesizing enzymes and hormone receptors in the brain.

The organizational/activational hypothesis of steroid hormone action on the brain was first proposed by Phoenix et al. (1959), in a seminal paper which revealed that the exposure to androgens during the early developmental period is essential for the presentation of androgen-induced male-specific behaviors at adulthood. These data obtained in Guinea pigs provided the first evidence that gonadal hormones exert a permanent/organizational effect during a critical period, corresponding to fetal and neonatal development (Knickmeyer and Baron-Cohen, 2006).

Another major breakthrough in steroid hormone research field has been represented by the demonstration that *de novo* steroid synthesis contributes to the establishment and maintenance of sex dimorphisms within the nervous system in both sexes, particularly in brain sites unrelated to reproduction (McCarthy et al., 2008; Schwarz and McCarthy, 2008). This pioneering discovery came from the observation that blood levels of steroid hormones do not necessarily overlap with their brain concentrations (Schumacher et al., 2003). Nowadays, extensive evidence, in a variety of species, supports this notion and steroids synthesized in the brain are commonly referred to as neurosteroids.

While overwhelming consensus has been reached on the contribution made by gonadally-produced sex steroids and neurosteroids to brain gender differences, it has become clear that not all sex differences can be explained by gonadal hormonal effects (Arnold, 2009; McCarthy and Arnold, 2011). Several studies conducted to identify other factors underlying, and contributing to, brain sex differences, point to differential neural expression of genes specifically located on the X and Y sex chromosomes as other major actors in the differentiation of male and female brains (Arnold, 2009; Davies and Wilkinson, 2006; Wolstenholme et al., 2013). To further complicate the topic, increasing evidence demonstrates that steroid hormones exert epigenetic effects on the developing nervous system to dictate adult sex differences in brain and behavior (Matsuda et al., 2012). These include modifications in DNA methylation, histone modification, genomic imprinting and microRNAs (McCarthy and Nugent, 2015). Moreover, it seems apparent that specific brain areas rely on different mechanisms to attain sex dimorphism (Brandt et al., 2013; Dean and McCarthy, 2008; McCarthy and Konkle, 2005), thus further corroborating the potential involvement of epigenetic regulation of steroid action in the brain.

3. Sexual dimorphism in abnormal brain development: exploring the role of genes and sex hormones interaction in human neurodevelopmental disorders

As discussed above, increasing evidence demonstrates a complex interaction between sex hormones and genetic and epigenetic factors in the establishment of sex differences in brain and behavior. The widespread differential susceptibility to pathology of males and females affected by neuropsychiatric diseases suggests a potential involvement of an abnormal genes and sex hormones interplay during brain development in this class of disorders (Hill et al., 2004; Kokras and Dalla, 2014; Mottron et al., 2015).

To shed light on this topic, this review will examine sex biases in human neurodevelopmental disorders from a clinical point of view, particularly focusing on those of well-established genetic origin, such as Rett syndrome, CDKL5-associated disorders, Fragile X and Down syndrome. Autism will be also addressed, given its paradigmatic role as a sex-biased neurodevelopmental disorder (Lai et al., 2015b). Current knowledge about sex differences in validated animal models for these disorders will be also explored. Given the increasing number of mouse models carrying mutations in genes relevant for this class of diseases, we will exploit this valuable tool to address the potential interplay between genes and sex hormones at the preclinical level.

3.1. Autism

Autism is a neurodevelopmental disorder characterized by restricted and repetitive patterns of behavior, interests, or activities, and deficits in social communication and interaction (APA, 2013). Males are diagnosed with this disease three to four times more commonly than females and a number of gender differences has been reported in this disorder, starting as early as the postnatal period (Baron-Cohen et al., 2011; Fombonne, 2005; Schaafsma and Pfaff, 2014; Werling and Geschwind, 2013) Such differences span from the onset and severity of symptoms, with females being more severely affected, to sex/gender differences in neuroanatomical and physiological endpoints (Lai et al., 2013; Mottron et al., 2015). Discoveries on this issue have been recently summarized in a special issue by *Molecular Autism*, 2015 (Lai et al., 2015a).

The “extreme male brain theory” of autism proposed by Baron-Cohen postulates that individuals suffering from disorders related