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Review

Biological factors underlying sex differences in neurological disorders: Focus on SRY

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ABSTRACT

The prevalence, age of onset, pathophysiology, and symptomatology of many neurological and neuropsychiatric conditions differ significantly between males and females. Females suffer more from mood disorders such as depression and anxiety, whereas males are more susceptible to deficits in the dopamine system including Parkinson's disease (PD), attention-deficit hyperactivity disorder (ADHD), schizophrenia, and autism spectrum disorders (ASD). Until recently, these sex differences have been explained solely by the neuroprotective actions of sex hormones in females. Emerging evidence however indicates that the sex chromosome genes (i.e. X- and Y-linked genes) also contribute to brain sex differences. In particular, the Y-chromosome gene, *SRY* (*Sex-determining Region on the Y chromosome*) is an interesting candidate as it is expressed in dopamine-abundant brain regions, where it regulates dopamine biosynthesis and dopamine-mediated functions such as voluntary movement in males. Furthermore, SRY expression is dysregulated in a toxin-induced model of PD, suggesting a role for SRY in the pathogenesis of DA cells. Taken together, these studies highlight the importance of understanding the interplay between sex-specific hormones and sex-specific genes in healthy and diseased brain. In particular, better understanding of regulation and function of *SRY* in the male brain could provide entirely novel and important insights into genetic factors involved in the susceptibility of men to neurological disorders, as well as development of novel sex-specific therapies.

Contents

Abbreviations: DA, dopamine; PD, Parkinson's disease; ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorders; SRY, sex-determining region on the Y chromosome; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; VTA, ventral tegmental area; TH, tyrosine hydroxylase; D1R, dopamine D1 receptor; D2R, dopamine D2 receptor; DAT, dopamine transporter; COMT, catechol-*O*-methyl transferase; MAO, monoamine oxidase; DDC, dopa decarboxylase; DBH, dopamine β-hydroxylase; VMAT, vesicular monoamine transporter; NA, noradrenaline; SHR, spontaneously hypertensive rat; 6-OHDA, 6-hydroxydopamine; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; GADD45γ, growth arrest and DNA damage gamma; GWAS, genome wide association studies.

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1. Introduction

Aside from generating distinct sexual reproductive behaviours, brain sex differences significantly influence brain anatomy, biochemistry, as well as various psychological and cognitive processes. Meta-analysis reviewing 20 years of research into brain structural differences revealed that males on average have 8–13% larger brain volumes compared to females (Ruigrok et al., 2014), although sexual dimorphisms of adult brain volumes are not diffusely spread across the brain but rather region specific (Goldstein et al., 2001). A diffusion tensor imaging (DTI) study showed sex differences in the structural connectome of the human brain, where the male brains are optimized for intra-hemispheric and female brains for inter-hemispheric communication (Ingalhalikar et al., 2014). Furthermore, genome-wide analysis performed in 137 human post mortem brains showed that 2.5% of genes are differentially expressed and spliced between males and females (Trabzuni et al., 2013). These fundamental sex differences in the anatomy and genetic network of the healthy brain are likely to underlie the pronounced sex differences in susceptibility, progression, symptom severity, and pathology of neurological disorders (Cahill, 2006; Cosgrove et al., 2007; Gillies and McArthur, 2010; McCarthy et al., 2012; Ngun et al., 2011). For example, females are more likely than males to develop depression, anxiety (Nolen-Hoeksema, 1987; Weissman et al., 1996) and Alzheimer's disease (Hebert et al., 2013), whilst males are more likely to be diagnosed with Parkinson's disease (PD) (Wooten et al., 2004), attention deficit hyperactivity disorder (ADHD) (Balint et al., 2009), and autism spectrum disorders (ASD) (Gillberg et al., 2006). Hence, better understanding of the biology underlying sex differences in the healthy and diseased brain will be vital for designing novel therapeutic agents that will have optimal effectiveness in each sex. Historically, the sex differences in neurological disorders have been explained by the protective actions of sex hormones in females (Auyeung et al., 2009; Gillies and McArthur, 2010; Riecher Rossler, 1994). However, emerging evidence suggests that genetic factors, in particular sex chromosome genes, also contribute to brain sex differences (Arnold et al., 2004; Beyer et al., 1992; Carruth et al., 2002; Dewing et al., 2003). Here we review studies of hormonal and genetic factors underlying the sex dimorphism in neurological disorders. We will contend that genetic factors play a far more important role than previously suspected. In particular, we highlight evidence that the Y-chromosome gene, *SRY*, regulates dopamine biochemistry and function in the male brain. Based on SRY expression in brain regions associated with the symptoms of DA-associated disorders, we speculate upon how dysregulation of *SRY* may be a contributing factor to male-susceptibility in disorders such as PD and ADHD.

2. Male bias in neurological disorders associated with dopamine

2.1. Dopamine mediates important physiological processes in the brain

Dopamine (DA) is a neurotransmitter that mediates a variety of important physiological processes such as voluntary movement, feeding, reward, sleep, attention, working memory and learning (Bjorklund and Dunnett, 2007b; Carlsson, 1987; Iversen, 2007). Maintenance of physiological levels of DA by various DA machineries is crucial for regulation of these processes. As summarized in Fig. 1A, DA is synthesized by a series of enzymatic reactions. L-Tyrosine, is converted into L-DOPA by the enzyme, tyrosine hydroxylase (TH). L-DOPA is converted to DA by the enzyme, dopa decarboxylase (DDC). In the presynaptic nerve terminal, the vesicular monoamine transporter (VMAT) sequesters DA into synaptic vesicles where DA is stored until an action potential occurs which releases DA into the synapse. DA itself is also used as precursor in the synthesis of the neurotransmitter noradrenaline (NA), as DA is converted into NA by the enzyme dopamine β-hydroxylase (DBH). DA exerts its action via the dopamine D1 receptor (D1R) or dopamine D2 receptor (D2R) on the postsynaptic target cell. The D1R family includes the DRD1 and DRD5 subtypes whilst the D2R family consists of the DRD2, DRD3, and DRD4 subtypes. The dopamine transporter (DAT), located at the presynaptic nerve terminal, controls the concentration of DA in the extracellular space by actively clearing extra-synaptic DA by re-uptake. Unbound extra-synaptic DA can also bind to presynaptic dopamine DRD2/DRD3 autoreceptors, which serves to maintain normal levels of synaptic DA by inhibition of DA synthesis and release. Cytosolic DA is directly broken down into inactive metabolites by the actions of catechol-*O*-methyl transferase (COMT) and monoamine oxidase (MAO), which has two isoforms MAO-A and MAO-B.

There are four major dopaminergic pathways in the brain – i.e. nigrostriatal, mesolimbic, mesocortical, and tuberoinfundibular pathway – which regulate various central functions. The nigrostriatal pathway transmits DA from the substantia nigra pars compacta (SNc) to the striatum for control of voluntary movement (Bjorklund and Dunnett, 2007a; Tsui and Isacson, 2011). Dopaminergic projections from the ventral tegmental area (VTA) to the limbic system (i.e. hypothalamus, hippocampus and amygdala), via the nucleus accumbens, form the mesolimbic pathway, which is important for motivation and reward-based learning (Bjorklund and Dunnett, 2007a; Gonzales et al., 2004). The mesocortical system originates from the VTA and transmits DA to the prefrontal cortex for executive functions, such as decision-making, cognitive and social behaviour (Bjorklund and Dunnett, 2007a; Robbins, 2000). Projections from the hypothalamus to the pituitary gland form the

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