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Sex-dependent mental illnesses and mitochondria

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ABSTRACT

The prevalence of some mental illnesses, including major depression, anxiety-, trauma-, and stress-related disorders, some substance use disorders, and later onset of schizophrenia, is higher in women than men. While the higher prevalence in women could simply be explained by socioeconomic determinants, such as income, social status, or cultural background, extensive studies show sex differences in biological, pharmacokinetic, and pharmacological factors contribute to females' vulnerability to these mental illnesses. In this review, we focus on estrogens, chronic stress, and neurotoxicity from behavioral, pharmacological, biological, and molecular perspectives to delineate the sex differences in these mental illnesses. Particularly, we investigate a possible role of mitochondrial function, including biosynthesis, bioenergetics, and signaling, on mediating the sex differences in psychiatric disorders.

1. Introduction

World Mental Health Surveys, directed by the World Health Organization (WHO), estimate that lifetime prevalence for Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) disorders, including anxiety, mood, and substance use disorders, ranges from 18.1–36.1% in the 28 countries participating in the surveys. The estimate of 12-months' prevalence for serious mental illnesses is up to 7% of the population in some countries (Kessler et al., 2009). In the United States, the National Survey on Drug Use and Health (NSDUH) estimates nearly 44 million adults aged 18 and older are suffering from mental illnesses, and 22 million from substance use disorders (SUD), every year (Karg et al., 2014).

The prevalence of some mental illnesses is sex-dependent. For example, men are more likely to suffer from alcohol and cocaine dependence, while women are more vulnerable to opioid and methamphetamine use disorders (Back et al., 2011; Hernandez-Avila et al., 2004; Keyes et al., 2008). Women are also more likely than men to suffer from many stress-related disorders, including generalized anxiety and post-traumatic stress disorders (PTSD) (Kessler et al., 1995; Olff et al., 2007; Wittchen and Hoyer, 2001). For major depression (MD), women have twice the prevalence of men (Kendler et al., 2003; Kessler et al., 1994; Piccinelli and Wilkinson, 2000). Further, women are more likely than men to suffer from schizophrenia (SZ) particularly at an older age (Abel et al., 2010; Meesters et al., 2012). These female-predominant mental illnesses could be explained simply due to socioeconomic determinants, such as income, social status, or cultural background (WHO, 2016). Yet both human and animal studies show clear sex differences in the biological and physiological effects of substances or stressors.

Mitochondria are organelles found in almost all eukaryotic cells. There are 3 major functions in mitochondria; biosynthesis, electron transport chain (ETC), and calcium (Ca^{2+}) uptake and signaling (Weinberg and Chandel, 2015). Biosynthesis produces a reduced form of nicotinamide adenine dinucleotide (NADH) by using acetyl coenzyme A in a tricarboxylic acid (TCA) cycle. NADH then enters the ETC and releases protons for the synthesis of adenosine triphosphate (ATP) by ATP synthase. The TCA cycle takes place in the mitochondrial matrix and indirectly mediates synthesis of macromolecules, such as amino acids, lipids and nucleotides. Mitochondrial Ca^{2+} levels are also involved in the regulation of ATP production, while bidirectional Ca^{2+} transport regulates Ca^{2+} homeostasis between cytosol and mitochondria (Duchen, 1999, 2000). Any dysfunctions in the maintenance of

Abbreviations: ATP, adenosine triphosphate; Bcl-2, anti-apoptotic B cell lymphoma 2; CNS, central nervous system; CORT, corticosterone; CPP, conditioned place preference; CRF, corticotropin releasing factor; CRFR, corticotropin releasing factor receptor; DA, dopamine; DSM, Diagnostic and Statistical Manual of Mental Disorders; ECS, extracellular space; ER, estrogen receptor; ETC, electron transport chain; FST, forced swim test; GABA, γ-aminobutyric acid; GAD, generalized anxiety disorder; GC, glucocorticoid; GR, glucocorticoid receptor; HPA, hypothalamic-pituitary-adrenal; HPG, hypothalamic-pituitary-gonadal; HRP, hormone replacement therapy; MBR, mitochondrial benzodiazepine receptor; MD, major depression; METH, methamphetamine; MOR, mu opioid receptor; mPFC, medial prefrontal cortex; mtDNA, mitochondrial DNA; NADH, nicotinamide adenine dinucleotide; NIDA, National Institute on Drug Abuse; NOS, nitrate oxygen species; NSDUH, National Survey on Drug Use and Health; OVX, ovariectomy; PTSD, post-traumatic stress disorders; ROS, reactive oxygen species; SERM, selective estrogen receptor modulators; Sig-1R, sigma-1 receptor; SUD, substance use disorders; TCA, tricarboxylic acid; UCP2, uncoupling protein 2; VMAT, vesicular monoamine transporter; WHO, World Health Organization; 5-HT, serotonin.

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Ca^{2+} balance in the mitochondria can lead to accumulation of reactive oxygen species (ROS) and nitrate oxygen species (NOS) (Duchen, 1999, 2000). Increased ROS/NOS is well documented in neurodegenerative disorders, such as Parkinson's, Alzheimer's, and Huntington's diseases, and multiple sclerosis (Abou-Sleiman et al., 2006; Beal, 1995, 1998). Also, a recent review article delineates the sex difference in various mitochondrial functions with respect to CNS diseases (Demarest and McCarthy, 2015).

In this review, we focus on mental illnesses that have a clear sex difference in prevalence; MD, SUD, anxiety, PTSD, and later onset of SZ. We review these illnesses from behavioral, neurochemical, neurobiological, and molecular perspectives, and discuss a possible role of mitochondrial dysfunction. As pointed out by the National Institutes of Health Office of Research on Women's Health, studies on females in biomedical and cell research are limited to date (Clayton and Collins, 2014; Prendergast et al., 2014). Accordingly, there are some limitations in research articles for this review as well.

2. MD

2.1. MD and estrogens

The lifetime prevalence of mood disorders, including MD, is substantially higher in women than in men (7.5% for women *vs*. 4.4% for men), beginning in adolescence and continuing throughout the lifespan (Karg et al., 2014; Piccinelli and Wilkinson, 2000). Part of this sex disparity, particularly for menopausal or postpartum depression, is an endocrine dysregulation of the hypothalamic pituitary gonadal (HPG) axis, decreasing circulating estrogens (Bloch et al., 2003; Cohen et al., 2006; Freeman et al., 2006). Likewise, we and others have shown a disruption of estrous cycle in animal models of depression, as demonstrated by extended non-ovulating days presumably secreting low estrogens (Dalla et al., 2005; Grippo et al., 2005; Rappeneau et al., 2016; Shimamoto et al., 2011). Alternately, removal of ovaries (ovariectomy, OVX) can induce depressive-like behaviors in rodents (Lagunas et al., 2010; Nakagawasai et al., 2009; Rachman et al., 1998), and the duration of OVX positively correlates with the severity of depressive-like symptoms (Lagunas et al., 2010; Walf et al., 2009). Estrogen supplementation has successfully alleviated depression-like symptoms in both human patients and OVX female animals (Berlanga and Flores-Ramos, 2006; Martenyi et al., 2001; Nakagawasai et al., 2009; Rachman et al., 1998; Romano-Torres and Fernandez-Guasti, 2010; Thase et al., 2005). Further, when combined with antidepressants, estrogens can potentiate the antidepressant effects (Mahmoud et al., 2016; Rasgon et al., 2007; Recamier-Carballo et al., 2012). These observations indicate that ovarian hormones critically mediate depressive-like symptoms. It should be noted, however, that some clinical studies show no effects of estrogen replacement therapy on reversing depressive-like symptoms for postmenopausal women (Almeida et al., 2006; Goldstein et al., 2005; Martel et al., 2009; Morrison et al., 2004; Pefanco et al., 2007; Schmidt and Rubinow, 2002).

2.2. Estrogens and mitochondria on MD

While the dysfunction of mitochondria has been implicated in MD (Rezin et al., 2009; Shao et al., 2008), no clinical evidence has indicated a link between estrogens and mitochondrial dysfunction in MD (Gardner and Boles, 2008a, 2008b; Gardner et al., 2003). Yet extensive *in vitro* studies demonstrate estrogens' protective role against mitochondrial oxidative stress. For instance, estrogens can directly block the impairment of TCA cycle, inhibit exogenous ROS from entering mitochondria, and prevent mitochondrial collapse due to membrane depolarization (Dykens et al., 2003; Nilsen and Brinton, 2002a, 2002b; Nilsen and Diaz Brinton, 2003; Simpkins et al., 2008; Wang, 2001; Wang et al., 2003). Furthermore, estrogens can directly facilitate mitochondrial respiratory function and ATP synthesis (Irwin et al., 2008; Zheng and Ramirez, 1999). In neurons, mitochondria exclusively express estrogen receptor β subtype (ERβ) (Yang et al., 2004). Interestingly, animal studies show that activation of ERβ can ameliorate depressive-like behaviors more than the activation of ERα (Walf and Frye, 2006; Walf et al., 2004). Alternatively, ERβ knockout mice fail to have ameliorated depressive-like behaviors (Rocha et al., 2005). Hence, mitochondrial ERβ may be the key substrate for mitochondrial dysfunction as an underlying mechanism for the sex difference in depressive-like symptoms (Fig. 1).

2.3. Stress-related hormones and mitochondria on MD

Clinical studies show that selected symptoms of MD, such as somatization, are positively correlated with reduced mitochondrial ATP production rate and their enzyme ratios in muscle tissues (Gardner and Boles, 2008a, 2008b; Gardner et al., 2003). With respect to brain, reduced cerebral blood flow and glucose metabolism in brain areas associated with executive function and motor movement are observed in some MD patients (for review see Videbech, 2000). Such reduced energy supply is an indication of mitochondrial dysfunction (Sims and Anderson, 2002). Also, an inhibition of the mitochondrial respiratory chain was observed in animals that were exposed to chronic stress (Rezin et al., 2008). The duration of such stress exposure correlated with the degree of decrease in mitochondrial enzymatic activity (Madrigal et al., 2001). Because chronic stress is the primary cause of the symptoms of MD (Anisman and Matheson, 2005; Radley et al., 2015), these observations indicate that chronic stress impairs mitochondrial function and may contribute to the symptomatology of MD.

Stress hormones, such as glucocorticoids, are known to impair mitochondrial function through signaling cascades. Animal studies show that chronic stress increases glucocorticoid receptor (GR) protein and cytochrome oxidase subunits in mitochondria, and activates a proapoptotic process by reducing mitochondrial anti-apoptotic molecules such as anti-apoptotic B cell lymphoma 2 (Bcl-2) and bcl-2-like protein 4 Bax proteins (Adzic et al., 2009; Djordjevic et al., 2009, 2010). Further, the activation of mitochondrial GR is shown to facilitate apoptotic processes in neural stem cells, which can be reversed by GR antagonist (Mutsaers and Tofighi, 2012). Similarly, repeated administration of corticosterone (CORT), a major stress hormone in rodents analogous to human cortisol, decreases anti-apoptotic molecules in mitochondria (Du et al., 2009a, 2009b). In this regard, one study shows that mitochondrial GR phosphorylation promoting pro-apoptotic signaling can be sex-dependent, such that chronic stress accumulates mitochondrial GR and increases cytochrome *c* oxidase more in females than in males (Adzic et al., 2013). Hence, it is possible that mitochondrial GR signaling may play a role in the sex difference of chronic stress-induced MD.

Corticotropin releasing factor (CRF) is a 41 amino acid-containing neuropeptide that mediates both brain and systemic responses to stress (Koob and Heinrichs, 1999; Rivier and Vale, 1983; Sutton et al., 1982; Vale et al., 1981). An increased CRF peptides has been observed in postmortem MD patients (Hartline et al., 1996; Holsboer, 1999a, 1999b). In this regard, female, but not male, mice lacking CRF receptor subtype 2 (CRFR2) spent increased time immobile during a forced swim test (FST), an indication of depressive-like symptoms (Bale and Vale, 2003). Similarly, female mice lacking urocortin-2, an endogenous agonist for CRFR2, also showed an increased immobility time in FST (Bale et al., 2003; Chen et al., 2006). Interestingly, the increased immobility time in female mice lacking CRFR2 can be reversed by antalarmin, a CRFR1 antagonist (Bale and Vale, 2003). These observations indicate that both CRFR1 and CRFR2 may mediate depressive-like symptoms synergizing with other molecules, particularly for females (Bale and Vale, 2003). Studies have shown that activation of CRFRs can prevent mitochondrial

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