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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.

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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 (Berlanger 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 (ER β) (Yang et al., 2004). Interestingly, animal studies show that activation of ER β can ameliorate depressive-like behaviors more than the activation of ER α (Walf and Frye, 2006; Walf et al., 2004). Alternatively, ER β knockout mice fail to have ameliorated depressive-like behaviors (Rocha et al., 2005). Hence, mitochondrial ER β 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

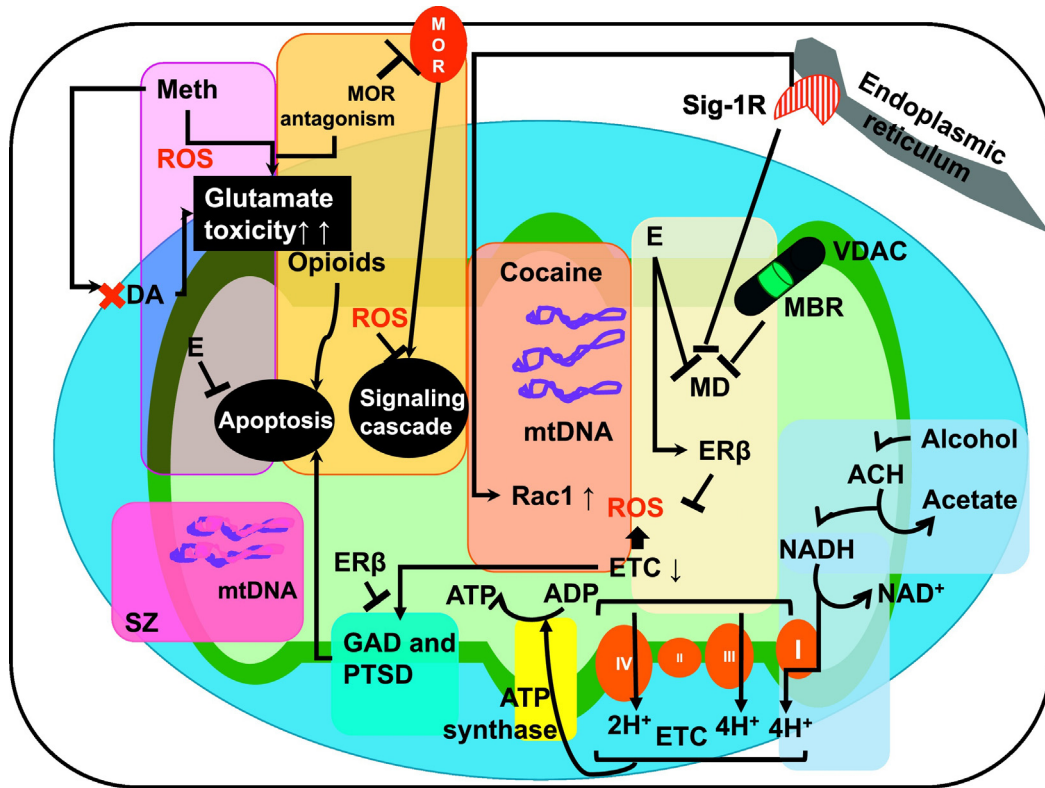


Fig. 1. An oversimplified schematic of a possible link between mitochondrial (dys)function and sex-dependent mental illnesses. **MD:** stress can interfere with electron transport chain (ETC) system and increase reactive oxidative species (ROS), inducing depressive-like behaviors. Estrogens (E), sigma1 receptors (Sig-1R), and mitochondrial benzodiazepine receptors (MBR) located at voltage-dependent anion channel (VDAC) can attenuate such behavioral deficits, possibly through estrogen receptor β subtype (ER β). **Alcohol:** The level of alcohol correlates with ROS levels due to dysregulation of ETC by increased NADH. Yet the role of ROS on facilitating alcohol reward is still unknown. **Cocaine:** Cocaine increases mitochondrial oxidative stress. Further, activation of Sig-1R can facilitate reward and potentiate relapse behaviors, possibly through increase of Rac1. Extinction from cocaine can increase mtDNA. **Opioids:** Opioids can disrupt mitochondrial anti-apoptotic pathway. ROS can impair MOR-dependent signaling cascade. MOR antagonism can increase glutamate excitotoxicity. **Meth:** Meth can induce ROS and apoptosis by first depleting DA contents then disinhibiting glutamatergic neurons, leading to glutamate excitotoxicity. E can attenuate Meth-induced apoptosis. **GAD and PTSD:** Both GAD and PTSD are associated with dysregulation in ETC system that induces ROS. E can alleviate symptoms of GAD and PTSD possibly via ER β . **SZ:** More mtDNA variants are seen in SZ men than women. Women have a higher prevalence of SZ during menopausal period.

oxidative stress from occurring, possibly by altering intracellular Ca^{2+} release (Bayatti and Behl, 2005; Lezoualc'h et al., 2000; Pedersen et al., 2002). Hence, it is likely that the disruption of CRF signaling cascade, potentially via CRFR2, can facilitate the mitochondrial oxidative stress leading to the expression of depressive-like symptoms. Yet it is not clear right now whether estrogens can mediate CRF's preventive action on oxidative stress at mitochondria.

2.4. Other substrates

Mitochondrial benzodiazepine receptor (MBR) is a type of peripheral benzodiazepine receptor located in the outer membrane of mitochondria (Casellas et al., 2002). One of the major roles of MBR is to assist permeability of the transition pore complex on the outer membrane of mitochondria (Fulda et al., 2010). Although the MBRs' function is more relevant to cancerous cells (Fulda et al., 2010), one study shows that a ligand for MBRs can induce anti-depressive-like behavior (Kita et al., 2004). Further, a dysfunction of MBR has been implicated in mitochondrial apoptosis (Decaudin et al., 2002; Okaro et al., 2002). In addition to MBRs, some studies have shown that activation of Sigma-1 receptor (Sig-1R), an endoplasmic reticulum-expressing chaperone protein, can reduce depressive-like behaviors, while the lack of Sig-1R conversely induced depressive-like behaviors in animals (Sabino et al., 2009; Urani et al., 2001). Interestingly, the depressive-like behaviors displayed by Sig-1R knockout mice were alleviated by estrogen administration (Sha et al., 2015). Sig-1R can maintain the health of mitochondria by exchanging ROS between the endoplasmic reticulum and

mitochondria (Fulda et al., 2010). Hence, Sig-1R may be a key substrate and target site for estrogens exerting a protective role for mitochondria.

3. SUD

3.1. Overview

Substance use disorders (SUD) cause significant impairments in the lives of individuals whose recurrent use of alcohol and/or drugs undermine accomplishing major responsibilities at work, school, or home (Karg et al., 2014). A diagnosis of SUD is made based on evidence of impaired control, health problems, disability, and risky use. Per NSDUH, the prevalence for alcohol and cocaine abuse is higher in men than in women, whereas abuse of opioids and methamphetamine is higher in women (Center for Behavioral Health Statistics and Quality, 2015). Animal studies show consistent biological and behavioral vulnerabilities for females in alcohol and drugs. In the following sections, sex differences in these domains will be described by drug type.

3.2. Alcohol

3.2.1. Sex difference and mitochondria

The deleterious effect of alcohol is largely dependent on strains, concentrations of alcohol ingested, and the models of consumption (Ceylan-Isik et al., 2010; Finn et al., 2004; Middaugh and Kelley, 1999; Middaugh et al., 1999; Taylor et al., 1990; van Haaren and Anderson, 1994). In any experimental scenario, estrogens do not appear to affect alcohol intake in females (Almeida et al., 1998; Cailhol and Mormede,

2001; Devaud et al., 1999). Rather, when calculated by weight, females have more ethanol in their system than males do (Juarez and Barrios de Tomasi, 1999; Piano et al., 2005). Furthermore, females have a slower emptying time for gastric contents, lower gastric and hepatic enzymes such as alcohol dehydrogenase and cytochrome P450, a smaller plasma volume, and a greater proportion of body fat relative to males (Gandhi et al., 2004). These observations indicate that alcohol stays in the body longer in females than in males, contributing to the sex difference of ethanol effects.

Mitochondrial oxidative stress has a positive correlation with levels of plasma alcohol in animals self-administering alcohol (Ivester et al., 2007). This is partially due to an increased NADH production at complex I in the process of oxidizing acetaldehyde, a first metabolite of alcohol (Quintanilla et al., 2005a; Quintanilla et al., 2005b) (Fig. 1). At this point, there is no direct evidence to suggest that the increase in oxidative stress can facilitate the rewarding process of alcohol. Yet some studies show that Sig-1R knockout mice consumed more alcohol than the wildtype (Su et al., 2010; Valenza et al., 2016). As previously described, Sig-1R can mediate the health of mitochondria through exchanging ROS between endoplasmic reticulum and mitochondria (Su et al., 2010). Furthermore, one study indicates a possible role for MBRs on sensitivity to alcohol that can be sex-dependent (Lin et al., 2015). Hence both Sig-1R and MBRs may mediate mitochondrial oxidative stress and possibly facilitate the rewarding process of alcohol.

3.2.2. CRF and mitochondria

Repeated exposure to stress can exaggerate drug reinforcement and relapse, including alcohol (Koob, 2008; Mantsch et al., 2016). CRF exaggerates ethanol self-administration, withdrawal-induced dysphoria, and reinstatement (Bruijnzeel et al., 2010; Eisenhardt et al., 2015; Finn et al., 2007; Le et al., 2000; Sarnyai et al., 2001; Sparta et al., 2009; Valdez et al., 2002; Zorrilla et al., 2014; Zorrilla et al., 2001). The CRF system can alter mitochondrial function, thus stress-induced alcohol intake may be mediated by CRF at mitochondria (Manoli et al., 2007).

3.3. Cocaine

3.3.1. Sex difference and estrogens

While the prevalence of cocaine dependence in humans is higher in men than in women (Center for Behavioral Health Statistics and Quality, 2015), animal studies consistently show that the pharmacological effects of cocaine are more severe in females than in males at every stage of cocaine addiction (see extensive review from: Anker and Carroll, 2010; Becker and Koob, 2016; Bobzean et al., 2010; Carroll et al., 2004; Hu et al., 2004; Lynch and Carroll, 1999; Lynch et al., 2002; Roth and Carroll, 2004). Both estrogens and selective estrogen receptor modulator (SERM) contribute to females' vulnerability to cocaine (Becker and Hu, 2008; Dalton et al., 1986; Larson et al., 2007; Larson et al., 2005; Lynch et al., 2001; Quinones-Jenab et al., 1999; Roberts et al., 1989; Wu et al., 2008). Further, stress can exaggerate the sex difference in cocaine-related behaviors for both humans and animals (Caillhol and Mormede, 1999; Feltenstein et al., 2011; Holly et al., 2012; Moran-Santa Maria et al., 2014)).

3.3.2. Rewarding and relapsing effects of cocaine and mitochondria

Cocaine can facilitate mitochondrial oxidative stress (for comprehensive review see: de Oliveira and Jardim, 2016; Lull et al., 2008), inducing toxic effects in both peripheral and CNS organs (Graziani et al., 2016; Kowalczyk-Pachel et al., 2016; Varga et al., 2015; Vitcheva et al., 2015). Yet the role of cocaine on facilitating reward or relapse behaviors with respect to mitochondrial oxidative stress is not clear. So far, it appears that mitochondrial oxidative stress and associated apoptosis can occur in animals who exhibited preference for cocaine in the conditioned place preference (CPP) test (Li et al., 2012). Further, a recent study shows increased copy numbers of mtDNA and gene expression in animals that went through an extinction training in an operant

cocaine self-administration paradigm (Sadakierska-Chudy et al., 2016) (Fig. 1). Extinction training is an experimental procedure that allows animals to press the lever previously associated with drug delivery but no longer is, and has been an effective protocol to attenuate relapsing behavior (Conklin and Tiffany, 2002; Havermans and Jansen, 2003; Reichel and Bevins, 2009). Collectively, repeated exposure to cocaine can induce the oxidative stress via mitochondria that may be normalized during the extinction training to prevent relapse.

3.3.3. Cocaine, Sig-1R, and mitochondria

The activation of Sig-1R can facilitate reward and relapse behaviors (Maurice and Romieu, 2004). While the exact mechanism is still unknown, a recent study shows that Sig-1R can directly act on small Rho-GTPases, such as Rac1, at mitochondria (Natsvlshvili et al., 2015). Rho-GTPases are known to mediate neuronal plasticity, including neuronal growth cone dynamics, dendritic spine formation, and axonal path finding (Luo, 2000; Natsvlshvili et al., 2015). Because cocaine can directly activate postsynaptic Sig-1R, it is possible that neuroplasticity, a foundation of addiction, is at least in part mediated by the activation of Rho-GTPases at mitochondria for cocaine (Kourrich et al., 2012; Maurice and Su, 2009) (Fig. 1).

3.4. Opioids

3.4.1. Sex difference

An estimated 26 to 36 million people use opioids worldwide (UNODC, 2014). In the United States, an estimated 2 million people are suffering from disorders from opioid pain relievers, including oxycodone, hydrocodone, and fentanyl, and half a million-people are suffering from heroin addiction, a synthetic compound of morphine (Karg et al., 2014). While the prevalence of heroin use disorders is higher in men than in women, the prevalence of pain relief disorders is significantly higher in women than in men (National Institute of Health, 2014). In animals, females self-administer heroin and morphine more than males, and acquire heroin faster on self-administration paradigms (Carroll et al., 2004; Cicero et al., 2003; Lynch and Carroll, 1999). Females also show a greater preference for morphine during CPP (Cicero et al., 2003; Karami and Zarrindast, 2008). Several opioid receptors, particularly the mu-opioid receptors (MORs), have been implicated in opioid dependence (for review see Chartoff and Connery, 2014).

3.4.2. Opioids and mitochondria

Like the substances described earlier, opioids can induce neurotoxic, oxidative, and mitochondrial apoptotic pathways. For example, *in vitro* studies demonstrate that opioids can disrupt mitochondrial antiapoptotic pathways by increasing the activation of caspase-3, cleavage of poly-ADP ribose polymerase (PARP), and DNA fragmentation (Cunha-Oliveira et al., 2007). Further, ROS can specifically impair the MOR-dependent signaling cascade but no other subtypes (Raut et al., 2006; Raut et al., 2007). Similarly, antagonism for MOR can enhance glutamate release, facilitating the glutamate excitotoxicity during opioid withdrawal (Aghajanian et al., 1994; Desole et al., 1996; Sepulveda et al., 1998; Sepulveda et al., 2004) (Fig. 1). While the role of mitochondrial oxidative stress on rewarding behaviors has not been tested, it is possible that MORs are key to mitochondrial oxidative stress mediating opioid addiction.

3.5. Methamphetamine (meth)

3.5.1. Sex difference

The prevalence of psychostimulant methamphetamine (meth) dependence disorder is slightly higher in women than in men (Dluzen and Liu, 2008; Pennell et al., 1999). Animal models also show some sex differences in the acquisition, intake, and a breakpoint for progressive ratio, as assessed by a self-administration paradigm (Carroll et al., 2004; Reichel et al., 2012). Unlike the other psychostimulant cocaine,

none of the addiction stages in meth self-administration appear to fluctuate by estrous cycle or be influenced by estrogens (Carroll et al., 2004; Gehrke et al., 2003).

3.5.2. Meth, neurotoxicity, and mitochondria

Meth and its demethylated form amphetamine are well-known neurotoxic agents which first deplete dopamine (DA) content at presynaptic vesicles then subsequently cause disinhibition of glutamatergic neurons (Matuszewich and Yamamoto, 2004; Quinton and Yamamoto, 2007; Raudensky and Yamamoto, 2007a, 2007b; Tata and Yamamoto, 2008). The disinhibition of glutamate subsequently activates downstream signaling cascades and facilitates neurodegenerative processes, such as the increase of ROS and NOS, inhibition of the mitochondrial ETC system, and the increase of cell death markers (Barbosa et al., 2015). Estrogens protect against the neurotoxic effects of meth by attenuating the DA depletion, improving the functional binding of DA and VMAT, and attenuating the mitochondrial apoptotic pathway (Bourque et al., 2011a, 2012; Bourque et al., 2011b; Dluzen, 2004; Dluzen and McDermott, 2002; Miller et al., 1998). However, meth's neurotoxicity appears to have little effect on its reward effect (Gehrke et al., 2003), or the rewarding effects induced by meth's neurotoxicity would extinguish sooner (Itzhak and Ali, 2002).

4. GAD and PTSD

4.1. Sex difference

The lifetime prevalence of generalized anxiety disorder (GAD) and post-traumatic stress disorder (PTSD) is higher in women than in men (Kessler et al., 1995; Olff et al., 2007; Wittchen and Hoyer, 2001). Both GAD and PTSD are associated with excessive worry and exaggerated fear reactions to disorder-specific stimuli in the absence of any actual danger, causing clinically significant distress and impairments (American Psychiatric Association, 2013). Like MD, disruption of the HPG axis plays a pivotal role in the sex difference in both GAD and PTSD (Bloch et al., 2003; Rocca et al., 2008; Rubinow and Schmidt, 1995). These anxiety symptoms can be alleviated by hormone replacement therapy (HRP) (Gambacciani et al., 2003; Heikkinen et al., 2006; Sherwin, 1991). It should be noted, however, that there has been an argument about the HRP treatment on reversing the anxiety symptoms (Frye, 2009; Kornstein et al., 2013; Resnick et al., 2009; Resnick et al., 2006; Welton et al., 2008).

4.2. Mitochondria, anxiety, and fear

Both human and animal studies show an association between the dysfunction of mitochondria and symptoms of anxiety and fear (Boles et al., 2005; Rice et al., 2010; Su et al., 2008). For example, a substitution of mtDNA that encodes genes involved in energy metabolism can increase anxiety in mice (Gimsa et al., 2009; Roubertoux et al., 2003). The anxiety-like responses are also increased in mice lacking a mitochondrial uncoupling protein 2 (UCP2), a protein that reduces oxidative stress, or in heterozygote mice that have reduced Bcl-2 protein expression (Einat et al., 2005; Gimsa et al., 2011). Increased anxiety-like behaviors are shown in mice with uncontrolled ROS production (Filiou et al., 2011; Rammal et al., 2008), and with dysregulation in ETC (Filiou et al., 2011; Filipovic et al., 2017; Garabadu et al., 2015; Rammal et al., 2008; Xing et al., 2013). By contrast, mice overexpressing an enzyme that catalyzes intracellular H₂O₂ (mitochondrial catalase enzyme) or Bcl-2 protein show reduced anxiety and fear-related conditioning learning (Olsen et al., 2013; Rondi-Reig et al., 1997). Further, antioxidant treatments at mitochondria reduce anxiety-like behaviors (Garabadu et al., 2015; Stefanova et al., 2010). Hence, mitochondrial dysfunction, particularly related to oxidative stress, can mediate anxiety-like and fear-related behaviors. In addition to oxidative stress, deficits in glycolysis, mitochondrial membrane potential, and alterations in

proteins and enzymes associated with mitochondrial import and transport such as adenosine diphosphate/ATP translocases and glutamate carriers are shown to induce anxiety-like and fear-related behaviors (Ditzen et al., 2006; Filiou et al., 2011; Filiou et al., 2014; Hovatta et al., 2005; Kromer et al., 2005; Weeber et al., 2002). Moreover, one study shows that estrogen administration can reduce fear conditioning through ER β (Chang et al., 2009). As previously described, ER β are the only estrogen receptor subtype expressed in neuronal mitochondria (Yang et al., 2004). Hence, ER β may be the key substrate for mitochondrial oxidative stress mediating anxiety or fear.

5. SZ

5.1. Sex difference and SZ

The lifetime prevalence of SZ is higher in men than in women (Abel et al., 2010). Yet the onset of SZ in older populations is more prevalent in women than in men (Hafner, 2003; Hafner and Nowotny, 1995). This later onset of SZ coincides with women's menopausal period (Seeman, 2012), suggesting that estrogens may contribute to the delay in the onset of SZ (Hafner, 2003; Hafner et al., 1993; Konnecke et al., 2000). Further, both clinical study and animal models of SZ show that estrogen treatments, including HRP or SERM, can reduce both positive and negative symptoms of SZ in females (Arad and Weiner, 2010, 2012; Begemann et al., 2012; Bergemann et al., 2007). Yet estrogen treatments for menopausal women appear to be effective only in reducing negative symptoms (Heringa et al., 2015). Since most animal models of SZ use adult males (for comprehensive review see Jones et al., 2011), few studies have identified biological and pharmacological mechanisms underlying estrogens' effects on reducing SZ-like symptoms in aged females. Future studies should pursue evidence on preclinical female models to advance sex-based treatment options for SZ.

5.2. Mitochondria, sex difference, and SZ

While extensive studies address the importance of dysfunction of mitochondria on SZ (for a comprehensive review see Clay et al., 2011), no studies indicate females' vulnerability to SZ with respect to the function (or dysfunction) of mitochondria, particularly at older age. Rather, studies have shown that more variants in mtDNA can increase oxidative stress in SZ men but not women, which may contribute to the higher prevalence of SZ in men than in women (Marchbanks et al., 2003; Mulcrone et al., 1995).

6. Conclusion

Mitochondrial function or dysfunction can be sex-dependent, which may determine sex differences in psychiatric pathologies. Impairments in mitochondria can be exaggerated by stress hormones, and may be alleviated by estrogens via ER β . Alternatively, a lack of estrogens may facilitate mitochondrial dysfunction, including oxidative stress. Yet reversing the psychiatric deficits by attenuating mitochondrial dysfunction is still at a nascent stage, partly due to a lack of animal models.

Contributors

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Conflicts of interest

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