Published in final edited form as:

Schizophr Res. 2017 September ; 187: 38–46. doi:10.1016/j.schres.2017.02.025.

Sex-dependent mental illnesses and mitochondria

Akiko Shimamoto* and Virginie Rappeneau

Department of Neuroscience and Pharmacology, School of Medicine, Meharry Medical College,
1005 Dr. D.B. Todd Jr. Blvd., Nashville, TN 37028-3599

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.

Keywords

Anxiety; major depression; mitochondria; sex difference; schizophrenia; substance use disorders

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., 2012).

*Corresponding author: Tel.: 615-327-6291, Fax: 615-327-6632, ashimamoto@mmc.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflicts of Interest

The authors declare that they have no financial interests or potential conflicts of interest.

Contributors

AS wrote Abstract, Introduction, and Sections 1, 2, 4, and 5. VR wrote Section 3.

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). 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 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.

1. MD

1.1 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., 2012; 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; Grippio 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 (Berlenga 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).

1.2. Estrogens and mitochondria on MD

While the dysfunction of mitochondria has been implicated in MD (Rezin GT 2009; Shao L 2008), no clinical evidence has indicated a link between estrogens and mitochondrial dysfunction in MD (Gardner and Boles, 2008a, b; 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 (Dyken et al., 2003; Nilsen and Brinton, 2002a, b; 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).

1.3 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, b; 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., 2000; 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,b). 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, b). 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 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.

1.4 Other substrates

Mitochondrial benzodiazepine receptor (MBR) is a type of peripheral benzodiazepine receptor located in the outer membrane of mitochondria (Casellas P 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.

2. SUD

2.1. 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 are 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.

2.2 Alcohol

2.2.1 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.

2.2.2 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).

2.3 Cocaine

2.3.1 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 (Cailhol and Mormede, 1999; Feltenstein et al., 2011; Holly et al., 2012; Moran-Santa Maria et al., 2014).

2.3.2. 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.

2.3.3. 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 (Natsvlishvili 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; Natsvlishvili 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).

2.4 Opioids

2.4.1 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., 2012). 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).

2.4.2 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.

2.5 Methamphetamine (meth)

2.5.1 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).

2.5.2 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, b; 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).

3. GAD and PTSD

3.1 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; Olf 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).

3.2 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., 2016; 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.

4. SZ

4.1. 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 H 2003; 1993; Konnecke R 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.

4.2 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 RM 2003; Mulcrone J 1995;).

5. 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.

Acknowledgments

The authors acknowledge Mr. Jared D. Elzey, Director, Services & Support Unit at Meharry Office for Research for his English edit.

Funding Source

This review was supported by National Institutes of Health Grants G12 MD007586 to Meharry Medical College. Scientific editing provided by the Meharry Office of Scientific Editing and Publications, S21 MD000104.

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

References

- Abel KM, Drake R, Goldstein JM. Sex differences in schizophrenia. International review of psychiatry. 2010; 22(5):417–428. [PubMed: 21047156]
- Abou-Sleiman PM, Muqit MM, Wood NW. Expanding insights of mitochondrial dysfunction in Parkinson's disease. Nature reviews Neuroscience. 2006; 7(3):207–219. [PubMed: 16495942]
- Adzic M, Djordjevic A, Demonacos C, Krstic-Demonacos M, Radojcic MB. The role of phosphorylated glucocorticoid receptor in mitochondrial functions and apoptotic signalling in brain tissue of stressed Wistar rats. The international journal of biochemistry & cell biology. 2009; 41(11):2181–2188. [PubMed: 19782950]
- Adzic M, Lukic I, Mitic M, Djordjevic J, Elakovic I, Djordjevic A, Krstic-Demonacos M, Matic G, Radojcic M. Brain region-and sex-specific modulation of mitochondrial glucocorticoid receptor phosphorylation in fluoxetine treated stressed rats: effects on energy metabolism. Psychoneuroendocrinology. 2013; 38(12):2914–2924. [PubMed: 23969420]

- Aghajanian GK, Kogan JH, Moghaddam B. Opiate withdrawal increases glutamate and aspartate efflux in the locus coeruleus: an in vivo microdialysis study. *Brain research*. 1994; 636(1):126–130. [PubMed: 7908850]
- Almeida OF, Shoaib M, Deicke J, Fischer D, Darwish MH, Patchev VK. Gender differences in ethanol preference and ingestion in rats. The role of the gonadal steroid environment. *The Journal of clinical investigation*. 1998; 101(12):2677–2685. [PubMed: 9637701]
- Almeida OP, Lautenschlager NT, Vasikaran S, Leedman P, Gelavis A, Flicker L. A 20-week randomized controlled trial of estradiol replacement therapy for women aged 70 years and older: effect on mood, cognition and quality of life. *Neurobiology of aging*. 2006; 27(1):141–149. [PubMed: 16298249]
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fifth. American Psychiatric Association; Arlington, VA: 2013.
- Anisman H, Matheson K. Stress, depression, and anhedonia: caveats concerning animal models. *Neuroscience and biobehavioral reviews*. 2005; 29(4–5):525–546. [PubMed: 15925696]
- Anker JJ, Carroll ME. Reinstatement of cocaine seeking induced by drugs, cues, and stress in adolescent and adult rats. *Psychopharmacology*. 2010; 208(2):211–222. [PubMed: 19953228]
- Arad M, Weiner I. Sex-dependent antipsychotic capacity of 17beta-estradiol in the latent inhibition model: a typical antipsychotic drug in both sexes, atypical antipsychotic drug in males. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology*. 2010; 35(11):2179–2192. [PubMed: 20613719]
- Arad M, Weiner I. Abnormally rapid reversal learning and reduced response to antipsychotic drugs following ovariectomy in female rats. *Psychoneuroendocrinology*. 2012; 37(2):200–212. [PubMed: 21723667]
- Back SE, Payne RL, Wahlquist AH, Carter RE, Stroud Z, Haynes L, Hillhouse M, Brady KT, Ling W. Comparative profiles of men and women with opioid dependence: results from a national multisite effectiveness trial. *The American journal of drug and alcohol abuse*. 2011; 37(5):313–323. [PubMed: 21854273]
- Bale TL, Giordano FJ, Vale WW. A new role for corticotropin-releasing factor receptor-2: suppression of vascularization. *Trends in cardiovascular medicine*. 2003; 13(2):68–71. [PubMed: 12586442]
- Bale TL, Vale WW. Increased depression-like behaviors in corticotropin-releasing factor receptor-2-deficient mice: sexually dichotomous responses. *The Journal of neuroscience: the official journal of the Society for Neuroscience*. 2003; 23(12):5295–5301. [PubMed: 12832554]
- Barbosa DJ, Capela JP, Feio-Azevedo R, Teixeira-Gomes A, Bastos Mde L, Carvalho F. Mitochondria: key players in the neurotoxic effects of amphetamines. *Archives of toxicology*. 2015; 89(10):1695–1725. [PubMed: 25743372]
- Bayatti N, Behl C. The neuroprotective actions of corticotropin releasing hormone. *Ageing research reviews*. 2005; 4(2):258–270. [PubMed: 16046283]
- Beal MF. Aging, energy, and oxidative stress in neurodegenerative diseases. *Annals of neurology*. 1995; 38(3):357–366. [PubMed: 7668820]
- Beal MF. Mitochondrial dysfunction in neurodegenerative diseases. *Biochimica et biophysica acta*. 1998; 1366(1–2):211–223. [PubMed: 9714810]
- Becker JB, Hu M. Sex differences in drug abuse. *Frontiers in neuroendocrinology*. 2008; 29(1):36–47. [PubMed: 17904621]
- Becker JB, Koob GF. Sex Differences in Animal Models: Focus on Addiction. *Pharmacological reviews*. 2016; 68(2):242–263. [PubMed: 26772794]
- Begemann MJ, Dekker CF, van Lunenburg M, Sommer IE. Estrogen augmentation in schizophrenia: a quantitative review of current evidence. *Schizophrenia research*. 2012; 141(2–3):179–184. [PubMed: 22998932]
- Bergemann N, Abu-Tair F, Strowitzki T. Estrogen in the treatment of late-onset schizophrenia. *Journal of clinical psychopharmacology*. 2007; 27(6):718–720. [PubMed: 18004148]
- Berlanga C, Flores-Ramos M. Different gender response to serotonergic and noradrenergic antidepressants. A comparative study of the efficacy of citalopram and reboxetine. *Journal of affective disorders*. 2006; 95(1–3):119–123. [PubMed: 16782204]

- Bloch M, Daly RC, Rubinow DR. Endocrine factors in the etiology of postpartum depression. *Comprehensive psychiatry*. 2003; 44(3):234–246. [PubMed: 12764712]
- Bobzean SA, Dennis TS, Addison BD, Perrotti LI. Influence of sex on reinstatement of cocaine-conditioned place preference. *Brain research bulletin*. 2010; 83(6):331–336. [PubMed: 20851744]
- Boles RG, Burnett BB, Gleditsch K, Wong S, Guedalia A, Kaariainen A, Eloed J, Stern A, Brumm V. A high predisposition to depression and anxiety in mothers and other matrilineal relatives of children with presumed maternally inherited mitochondrial disorders. *American journal of medical genetics Part B, Neuropsychiatric genetics: the official publication of the International Society of Psychiatric Genetics*. 2005; 137B(1):20–24.
- Bourque M, Dluzen DE, Di Paolo T. Male/Female differences in neuroprotection and neuromodulation of brain dopamine. *Frontiers in endocrinology*. 2011a; 2:35. [PubMed: 22654803]
- Bourque M, Dluzen DE, Di Paolo T. Sex and temporally-dependent effects of methamphetamine toxicity on dopamine markers and signaling pathways. *Neuropharmacology*. 2012; 62(7):2363–2372. [PubMed: 22369785]
- Bourque M, Liu B, Dluzen DE, Di Paolo T. Sex differences in methamphetamine toxicity in mice: effect on brain dopamine signaling pathways. *Psychoneuroendocrinology*. 2011b; 36(7):955–969. [PubMed: 21236583]
- Bruijnzeel AW, Small E, Pasek TM, Yamada H. Corticotropin-releasing factor mediates the dysphoria-like state associated with alcohol withdrawal in rats. *Behavioural brain research*. 2010; 210(2):288–291. [PubMed: 20193713]
- Cailhol S, Mormede P. Strain and sex differences in the locomotor response and behavioral sensitization to cocaine in hyperactive rats. *Brain research*. 1999; 842(1):200–205. [PubMed: 10526110]
- Cailhol S, Mormede P. Sex and strain differences in ethanol drinking: effects of gonadectomy. *Alcoholism, clinical and experimental research*. 2001; 25(4):594–599.
- Carroll ME, Lynch WJ, Roth ME, Morgan AD, Cosgrove KP. Sex and estrogen influence drug abuse. *Trends in pharmacological sciences*. 2004; 25(5):273–279. [PubMed: 15120494]
- Casellas P, Galiegue S, Basile AS. Peripheral benzodiazepine receptors and mitochondrial function. *Neurochemistry international*. 2002; 40(6):475–486. [PubMed: 11850104]
- Center for Behavioral Health Statistics and Quality. Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health. 2015. HHS Publication No. SMA 154927, NSDUH Series H-50
- Ceylan-Isik AF, McBride SM, Ren J. Sex difference in alcoholism: who is at a greater risk for development of alcoholic complication? *Life sciences*. 2010; 87(5–6):133–138. [PubMed: 20598716]
- Chang YJ, Yang CH, Liang YC, Yeh CM, Huang CC, Hsu KS. Estrogen modulates sexually dimorphic contextual fear extinction in rats through estrogen receptor beta. *Hippocampus*. 2009; 19(11):1142–1150. [PubMed: 19338017]
- Chartoff EH, Connery HS. It's MORE exciting than mu: crosstalk between mu opioid receptors and glutamatergic transmission in the mesolimbic dopamine system. *Frontiers in pharmacology*. 2014; 5:116. [PubMed: 24904419]
- Chen A, Zorrilla E, Smith S, Rousso D, Levy C, Vaughan J, Donaldson C, Roberts A, Lee KF, Vale W. Urocortin 2-deficient mice exhibit gender-specific alterations in circadian hypothalamus-pituitary-adrenal axis and depressive-like behavior. *The Journal of neuroscience: the official journal of the Society for Neuroscience*. 2006; 26(20):5500–5510. [PubMed: 16707802]
- Cicero TJ, Aylward SC, Meyer ER. Gender differences in the intravenous self-administration of mu opiate agonists. *Pharmacology, biochemistry, and behavior*. 2003; 74(3):541–549.
- Clay HB, Sullivan S, Konradi C. Mitochondrial dysfunction and pathology in bipolar disorder and schizophrenia. *International journal of developmental neuroscience: the official journal of the International Society for Developmental Neuroscience*. 2011; 29(3):311–324. [PubMed: 20833242]
- Clayton JA, Collins FS. Policy: NIH to balance sex in cell and animal studies. *Nature*. 2014; 509(7500):282–283. [PubMed: 24834516]

- Cohen LS, Soares CN, Vitonis AF, Otto MW, Harlow BL. Risk for new onset of depression during the menopausal transition: the Harvard study of moods and cycles. *Archives of general psychiatry*. 2006; 63(4):385–390. [PubMed: 16585467]
- Conklin CA, Tiffany ST. Applying extinction research and theory to cue-exposure addiction treatments. *Addiction*. 2002; 97(2):155–167. [PubMed: 11860387]
- Cunha-Oliveira T, Rego AC, Garrido J, Borges F, Macedo T, Oliveira CR. Street heroin induces mitochondrial dysfunction and apoptosis in rat cortical neurons. *Journal of neurochemistry*. 2007; 101(2):543–554. [PubMed: 17250679]
- Dalla C, Antoniou K, Drossopoulou G, Xagoraris M, Kokras N, Sfikakis A, Papadopoulou-Daifoti Z. Chronic mild stress impact: are females more vulnerable? *Neuroscience*. 2005; 135(3):703–714. [PubMed: 16125862]
- Dalton JC, Vickers GJ, Roberts DC. Increased self-administration of cocaine following haloperidol: sex-dependent effects of the antiestrogen tamoxifen. *Pharmacology, biochemistry, and behavior*. 1986; 25(3):497–501.
- Decaudin D, Castedo M, Nemati F, Beurdeley-Thomas A, De Pinieux G, Caron A, Pouillart P, Wijdenes J, Rouillard D, Kroemer G, Poupon MF. Peripheral benzodiazepine receptor ligands reverse apoptosis resistance of cancer cells in vitro and in vivo. *Cancer research*. 2002; 62(5):1388–1393. [PubMed: 11888910]
- Demarest TG, McCarthy MM. Sex differences in mitochondrial (dys)function: Implications for neuroprotection. *Journal of bioenergetics and biomembranes*. 2015; 47(1–2):173–188. [PubMed: 25293493]
- de Oliveira MR, Jardim FR. Cocaine and mitochondria-related signaling in the brain: A mechanistic view and future directions. *Neurochemistry international*. 2016; 92:58–66. [PubMed: 26707813]
- Desole MS, Esposito G, Fresu L, Migheli R, Enrico P, Mura MA, De Natale G, Miele E, Miele M. Effects of morphine treatment and withdrawal on striatal and limbic monoaminergic activity and ascorbic acid oxidation in the rat. *Brain research*. 1996; 723(1–2):154–161. [PubMed: 8813393]
- Devaud LL, Matthews DB, Morrow AL. Gender impacts behavioral and neurochemical adaptations in ethanol-dependent rats. *Pharmacology, biochemistry, and behavior*. 1999; 64(4):841–849.
- Ditzen C, Jastorff AM, Kessler MS, Bunc M, Teplytska L, Erhardt A, Kromer SA, Varadarajulu J, Targosz BS, Sayan-Ayata EF, Holsboer F, Landgraf R, Turck CW. Protein biomarkers in a mouse model of extremes in trait anxiety. *Molecular & cellular proteomics: MCP*. 2006; 5(10):1914–1920. [PubMed: 16775081]
- Djordjevic A, Adzic M, Djordjevic J, Radojcic MB. Chronic social isolation is related to both upregulation of plasticity genes and initiation of proapoptotic signaling in Wistar rat hippocampus. *Journal of neural transmission*. 2009; 116(12):1579–1589. [PubMed: 19669692]
- Djordjevic A, Adzic M, Djordjevic J, Radojcic MB. Chronic social isolation suppresses proplastic response and promotes proapoptotic signalling in prefrontal cortex of Wistar rats. *Journal of neuroscience research*. 2010; 88(11):2524–2533. [PubMed: 20623537]
- Dluzen DE. The effect of gender and the neurotrophin, BDNF, upon methamphetamine-induced neurotoxicity of the nigrostriatal dopaminergic system in mice. *Neuroscience letters*. 2004; 359(3):135–138. [PubMed: 15050682]
- Dluzen DE, Liu B. Gender differences in methamphetamine use and responses: a review. *Gender medicine*. 2008; 5(1):24–35. [PubMed: 18420163]
- Dluzen DE, McDermott JL. Estrogen, anti-estrogen, and gender: differences in methamphetamine neurotoxicity. *Annals of the New York Academy of Sciences*. 2002; 965:136–156. [PubMed: 12105091]
- Du J, McEwen B, Manji HK. Glucocorticoid receptors modulate mitochondrial function: A novel mechanism for neuroprotection. *Communicative & integrative biology*. 2009a; 2(4):350–352. [PubMed: 19721888]
- Du J, Wang Y, Hunter R, Wei Y, Blumenthal R, Falke C, Khairova R, Zhou R, Yuan P, Machado-Vieira R, McEwen BS, Manji HK. Dynamic regulation of mitochondrial function by glucocorticoids. *Proceedings of the National Academy of Sciences of the United States of America*. 2009b; 106(9):3543–3548. [PubMed: 19202080]

- Duchen MR. Contributions of mitochondria to animal physiology: from homeostatic sensor to calcium signalling and cell death. *The Journal of physiology*. 1999; 516(Pt 1):1–17. [PubMed: 10066918]
- Duchen MR. Mitochondria and Ca(2+) in cell physiology and pathophysiology. *Cell calcium*. 2000; 28(5–6):339–348. [PubMed: 11115373]
- Dyken JA, Simpkins JW, Wang J, Gordon K. Polycyclic phenols, estrogens and neuroprotection: a proposed mitochondrial mechanism. *Experimental gerontology*. 2003; 38(1–2):101–107. [PubMed: 12543267]
- Einat H, Yuan P, Manji HK. Increased anxiety-like behaviors and mitochondrial dysfunction in mice with targeted mutation of the Bcl-2 gene: further support for the involvement of mitochondrial function in anxiety disorders. *Behavioural brain research*. 2005; 165(2):172–180. [PubMed: 16095731]
- Eisenhardt M, Hansson AC, Spanagel R, Bilbao A. Chronic intermittent ethanol exposure in mice leads to an up-regulation of CRH/CRHR1 signaling. *Alcoholism, clinical and experimental research*. 2015; 39(4):752–762.
- Feltenstein MW, Henderson AR, See RE. Enhancement of cue-induced reinstatement of cocaine-seeking in rats by yohimbine: sex differences and the role of the estrous cycle. *Psychopharmacology*. 2011; 216(1):53–62. [PubMed: 21308466]
- Filiou MD, Asara JM, Nussbaumer M, Teplytska L, Landgraf R, Turck CW. Behavioral extremes of trait anxiety in mice are characterized by distinct metabolic profiles. *Journal of psychiatric research*. 2014; 58:115–122. [PubMed: 25124548]
- Filiou MD, Zhang Y, Teplytska L, Reckow S, Gormanns P, Maccarrone G, Frank E, Kessler MS, Hambach B, Nussbaumer M, Bunck M, Ludwig T, Yassouridis A, Holsboer F, Landgraf R, Turck CW. Proteomics and metabolomics analysis of a trait anxiety mouse model reveals divergent mitochondrial pathways. *Biological psychiatry*. 2011; 70(11):1074–1082. [PubMed: 21791337]
- Filipovic D, Todorovic N, Bernardi RE, Gass P. Oxidative and nitrosative stress pathways in the brain of socially isolated adult male rats demonstrating depressive-and anxiety-like symptoms. *Brain structure & function*. 2016
- Finn DA, Long SL, Tanchuck MA, Crabbe JC. Interaction of chronic ethanol exposure and finasteride: sex and strain differences. *Pharmacology, biochemistry, and behavior*. 2004; 78(3):435–443.
- Finn DA, Snelling C, Fretwell AM, Tanchuck MA, Underwood L, Cole M, Crabbe JC, Roberts AJ. Increased drinking during withdrawal from intermittent ethanol exposure is blocked by the CRF receptor antagonist D-Phe-CRF(12–41). *Alcoholism, clinical and experimental research*. 2007; 31(6):939–949.
- Freeman EW, Sammel MD, Lin H, Nelson DB. Associations of hormones and menopausal status with depressed mood in women with no history of depression. *Archives of general psychiatry*. 2006; 63(4):375–382. [PubMed: 16585466]
- Frye CA. Steroids, reproductive endocrine function, and affect. A review *Minerva ginecologica*. 2009; 61(6):541–562. [PubMed: 19942840]
- Fulda S, Galluzzi L, Kroemer G. Targeting mitochondria for cancer therapy. *Nature reviews Drug discovery*. 2010; 9(6):447–464. [PubMed: 20467424]
- Gambacciani M, Ciaponi M, Cappagli B, Monteleone P, Benussi C, Bevilacqua G, Genazzani AR. Effects of low-dose, continuous combined estradiol and noretisterone acetate on menopausal quality of life in early postmenopausal women. *Maturitas*. 2003; 44(2):157–163. [PubMed: 12590012]
- Gandhi M, Aweeka F, Greenblatt RM, Blaschke TF. Sex differences in pharmacokinetics and pharmacodynamics. *Annual review of pharmacology and toxicology*. 2004; 44:499–523.
- Garabadu D, Ahmad A, Krishnamurthy S. Risperidone Attenuates Modified Stress-Re-stress Paradigm-Induced Mitochondrial Dysfunction and Apoptosis in Rats Exhibiting Post-traumatic Stress Disorder-Like Symptoms. *Journal of molecular neuroscience: MN*. 2015; 56(2):299–312. [PubMed: 25750029]
- Gardner A, Boles RG. Mitochondrial energy depletion in depression with somatization. *Psychotherapy and psychosomatics*. 2008a; 77(2):127–129. [PubMed: 18230947]
- Gardner A, Boles RG. Symptoms of somatization as a rapid screening tool for mitochondrial dysfunction in depression. *BioPsychoSocial medicine*. 2008b; 2:7. [PubMed: 18294386]

- Gardner A, Johansson A, Wibom R, Nennesmo I, von Döbeln U, Hagenfeldt L, Hallström T. Alterations of mitochondrial function and correlations with personality traits in selected major depressive disorder patients. *Journal of affective disorders*. 2003; 76(1–3):55–68. [PubMed: 12943934]
- Gehrke BJ, Harrod SB, Cass WA, Bardo MT. The effect of neurotoxic doses of methamphetamine on methamphetamine-conditioned place preference in rats. *Psychopharmacology*. 2003; 166(3):249–257. [PubMed: 12589519]
- Gimsa U, Kanitz E, Otten W, Aheng C, Tuchscherer M, Ricquier D, Miroux B, Ibrahim SM. Alterations in anxiety-like behavior following knockout of the uncoupling protein 2 (ucp2) gene in mice. *Life sciences*. 2011; 89(19–20):677–684. [PubMed: 21878341]
- Gimsa U, Kanitz E, Otten W, Ibrahim SM. Behavior and stress reactivity in mouse strains with mitochondrial DNA variations. *Annals of the New York Academy of Sciences*. 2009; 1153:131–138. [PubMed: 19236336]
- Goldstein KM, Harpole LH, Stechuchak KM, Coffman CJ, Bosworth HB, Steffens DC, Bastian LA. Hormone therapy does not affect depression severity in older women. *The American journal of geriatric psychiatry: official journal of the American Association for Geriatric Psychiatry*. 2005; 13(7):616–623. [PubMed: 16009738]
- Graziani M, Antonilli L, Togni AR, Grassi MC, Badiani A, Saso L. Cardiovascular and Hepatic Toxicity of Cocaine: Potential Beneficial Effects of Modulators of Oxidative Stress. *Oxidative medicine and cellular longevity*. 2016; 2016:8408479. [PubMed: 26823954]
- Grippio AJ, Sullivan NR, Damjanoska KJ, Crane JW, Carrasco GA, Shi J, Chen Z, Garcia F, Muma NA, Van de Kar LD. Chronic mild stress induces behavioral and physiological changes, and may alter serotonin 1A receptor function, in male and cycling female rats. *Psychopharmacology*. 2005; 179(4):769–780. [PubMed: 15619113]
- Hafner H. Gender differences in schizophrenia. *Psychoneuroendocrinology* 28 Suppl. 2003; 2:17–54.
- Hafner H, Maurer K, Löffler W, Riecher-Rössler A. The influence of age and sex on the onset and early course of schizophrenia. *The British journal of psychiatry: the journal of mental science*. 1993; 162:80–86. [PubMed: 8425144]
- Hafner H, Nowotny B. Epidemiology of early-onset schizophrenia. *European archives of psychiatry and clinical neuroscience*. 1995; 245(2):80–92. [PubMed: 7654792]
- Hartline KM, Owens MJ, Nemeroff CB. Postmortem and cerebrospinal fluid studies of corticotropin-releasing factor in humans. *Annals of the New York Academy of Sciences*. 1996; 780:96–105. [PubMed: 8602742]
- Havermans RC, Jansen AT. Increasing the efficacy of cue exposure treatment in preventing relapse of addictive behavior. *Addictive behaviors*. 2003; 28(5):989–994. [PubMed: 12788271]
- Heikkinen J, Vaheiri R, Timonen U. A 10-year follow-up of postmenopausal women on long-term continuous combined hormone replacement therapy: Update of safety and quality-of-life findings. *The journal of the British Menopause Society*. 2006; 12(3):115–125. [PubMed: 16953985]
- Heringa SM, Begemann MJ, Goverde AJ, Sommer IE. Sex hormones and oxytocin augmentation strategies in schizophrenia: A quantitative review. *Schizophrenia research*. 2015; 168(3):603–613. [PubMed: 25914107]
- Hernandez-Avila CA, Rounsaville BJ, Kranzler HR. Opioid-, cannabis- and alcohol-dependent women show more rapid progression to substance abuse treatment. *Drug and alcohol dependence*. 2004; 74(3):265–272. [PubMed: 15194204]
- Holly EN, Shimamoto A, Debold JF, Miczek KA. Sex differences in behavioral and neural cross-sensitization and escalated cocaine taking as a result of episodic social defeat stress in rats. *Psychopharmacology*. 2012; 224(1):179–188. [PubMed: 22926005]
- Holsboer F. Neuroendocrine studies and antidepressant drug development. *Seishin shinkeigaku zasshi = Psychiatria et neurologia Japonica*. 1999a; 101(9):711–716. [PubMed: 10586637]
- Holsboer F. The rationale for corticotropin-releasing hormone receptor (CRH-R) antagonists to treat depression and anxiety. *Journal of psychiatric research*. 1999b; 33(3):181–214. [PubMed: 10367986]

- Hovatta I, Tennant RS, Helton R, Marr RA, Singer O, Redwine JM, Ellison JA, Schadt EE, Verma IM, Lockhart DJ, Barlow C. Glyoxalase 1 and glutathione reductase 1 regulate anxiety in mice. *Nature*. 2005; 438(7068):662–666. [PubMed: 16244648]
- Hu M, Crombag HS, Robinson TE, Becker JB. Biological basis of sex differences in the propensity to self-administer cocaine. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology*. 2004; 29(1):81–85. [PubMed: 12955098]
- Irwin RW, Yao J, Hamilton RT, Cadenas E, Brinton RD, Nilsen J. Progesterone and estrogen regulate oxidative metabolism in brain mitochondria. *Endocrinology*. 2008; 149(6):3167–3175. [PubMed: 18292191]
- Itzhak Y, Ali SF. Behavioral consequences of methamphetamine-induced neurotoxicity in mice: relevance to the psychopathology of methamphetamine addiction. *Annals of the New York Academy of Sciences*. 2002; 965:127–135. [PubMed: 12105090]
- Ivester P, Roberts LJ 2nd, Young T, Stafforini D, Vivian J, Lees C, Young J, Daunais J, Friedman D, Rippe RA, Parsons CJ, Grant KA, Cunningham C. Ethanol self-administration and alterations in the livers of the cynomolgus monkey, *Macaca fascicularis*. *Alcoholism, clinical and experimental research*. 2007; 31(1):144–155.
- Jones CA, Watson DJ, Fone KC. Animal models of schizophrenia. *British journal of pharmacology*. 2011; 164(4):1162–1194. [PubMed: 21449915]
- Juarez J, Barrios de Tomasi E. Sex differences in alcohol drinking patterns during forced and voluntary consumption in rats. *Alcohol*. 1999; 19(1):15–22. [PubMed: 10487383]
- Karami M, Zarrindast MR. Morphine sex-dependently induced place conditioning in adult Wistar rats. *European journal of pharmacology*. 2008; 582(1–3):78–87. [PubMed: 18191832]
- Karg, SR., Bose, J., Batts, KR., Forman-Hoffman, VL., Liao, D., Hirsch, E., Pemberton, MR., Colpe, LJ., Hedden, SL. Past Year Mental Disorders among Adults in the United States: Results from the 2008–2012. Mental Health Surveillance Study, Center for Behavioral Health Statistics and Quality, SAMHSA; 2014.
- Kendler KS, Prescott CA, Myers J, Neale MC. The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Archives of general psychiatry*. 2003; 60(9):929–937. [PubMed: 12963675]
- Kessler RC, Aguilar-Gaxiola S, Alonso J, Chatterji S, Lee S, Ormel J, Ustun TB, Wang PS. The global burden of mental disorders: an update from the WHO World Mental Health (WMH) surveys. *Epidemiologia e psichiatria sociale*. 2009; 18(1):23–33. [PubMed: 19378696]
- Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Archives of general psychiatry*. 1994; 51(1):8–19. [PubMed: 8279933]
- Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. *Archives of general psychiatry*. 1995; 52(12):1048–1060. [PubMed: 7492257]
- Keyes KM, Grant BF, Hasin DS. Evidence for a closing gender gap in alcohol use, abuse, and dependence in the United States population. *Drug and alcohol dependence*. 2008; 93(1–2):21–29. [PubMed: 17980512]
- Kita A, Kohayakawa H, Kinoshita T, Ochi Y, Nakamichi K, Kurumiya S, Furukawa K, Oka M. Antianxiety and antidepressant-like effects of AC-5216, a novel mitochondrial benzodiazepine receptor ligand. *British journal of pharmacology*. 2004; 142(7):1059–1072. [PubMed: 15249420]
- Konnecke R, Hafner H, Maurer K, Löffler W, an der Heiden W. Main risk factors for schizophrenia: increased familial loading and pre-and peri-natal complications antagonize the protective effect of oestrogen in women. *Schizophrenia research*. 2000; 44(1):81–93. [PubMed: 10867314]
- Koob GF. A role for brain stress systems in addiction. *Neuron*. 2008; 59(1):11–34. [PubMed: 18614026]
- Koob GF, Heinrichs SC. A role for corticotropin releasing factor and urocortin in behavioral responses to stressors. *Brain research*. 1999; 848(1–2):141–152. [PubMed: 10612706]
- Kornstein SG, Toups M, Rush AJ, Wisniewski SR, Thase ME, Luther J, Warden D, Fava M, Trivedi MH. Do menopausal status and use of hormone therapy affect antidepressant treatment response?

Findings from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. *Journal of women's health*. 2013; 22(2):121–131.

- Kourrich S, Su TP, Fujimoto M, Bonci A. The sigma-1 receptor: roles in neuronal plasticity and disease. *Trends in neurosciences*. 2012; 35(12):762–771. [PubMed: 23102998]
- Kowalczyk-Pachel D, Iciek M, Wydra K, Nowak E, Gorny M, Filip M, Wlodek L, Lorenc-Koci E. Cysteine Metabolism and Oxidative Processes in the Rat Liver and Kidney after Acute and Repeated Cocaine Treatment. *PloS one*. 2016; 11(1):e0147238. [PubMed: 26808533]
- Kromer SA, Kessler MS, Milfay D, Birg IN, Bunck M, Czibere L, Panhuysen M, Putz B, Deussing JM, Holsboer F, Landgraf R, Turck CW. Identification of glyoxalase-I as a protein marker in a mouse model of extremes in trait anxiety. *The Journal of neuroscience: the official journal of the Society for Neuroscience*. 2005; 25(17):4375–4384. [PubMed: 15858064]
- Lagunas N, Calmarza-Font I, Diz-Chaves Y, Garcia-Segura LM. Long-term ovariectomy enhances anxiety and depressive-like behaviors in mice submitted to chronic unpredictable stress. *Hormones and behavior*. 2010; 58(5):786–791. [PubMed: 20691693]
- Larson EB, Anker JJ, Gliddon LA, Fons KS, Carroll ME. Effects of estrogen and progesterone on the escalation of cocaine self-administration in female rats during extended access. *Experimental and clinical psychopharmacology*. 2007; 15(5):461–471. [PubMed: 17924780]
- Larson EB, Roth ME, Anker JJ, Carroll ME. Effect of short-vs. long-term estrogen on reinstatement of cocaine-seeking behavior in female rats. *Pharmacology, biochemistry, and behavior*. 2005; 82(1): 98–108.
- Le AD, Harding S, Juzysch W, Watchus J, Shalev U, Shaham Y. The role of corticotrophin-releasing factor in stress-induced relapse to alcohol-seeking behavior in rats. *Psychopharmacology*. 2000; 150(3):317–324. [PubMed: 10923760]
- Lezoualc'h F, Engert S, Berning B, Behl C. Corticotropin-releasing hormone-mediated neuroprotection against oxidative stress is associated with the increased release of non-amyloidogenic amyloid beta precursor protein and with the suppression of nuclear factor-kappaB. *Molecular endocrinology*. 2000; 14(1):147–159. [PubMed: 10628754]
- Li Y, Yan GY, Zhou JQ, Bu Q, Deng PC, Yang YZ, Lv L, Deng Y, Zhao JX, Shao X, Zhu RM, Huang YN, Zhao YL, Cen XB. (1)H NMR-based metabonomics in brain nucleus accumbens and striatum following repeated cocaine treatment in rats. *Neuroscience*. 2012; 218:196–205. [PubMed: 22609933]
- Lin R, Rittenhouse D, Sweeney K, Potluri P, Wallace DC. TSPO, a Mitochondrial Outer Membrane Protein, Controls Ethanol-Related Behaviors in *Drosophila*. *PLoS genetics*. 2015; 11(8):e1005366. [PubMed: 26241038]
- Lull ME, Freeman WM, Vrana KE, Mash DC. Correlating human and animal studies of cocaine abuse and gene expression. *Annals of the New York Academy of Sciences*. 2008; 1141:58–75. [PubMed: 18991951]
- Luo L. Rho GTPases in neuronal morphogenesis. *Nature reviews Neuroscience*. 2000; 1(3):173–180. [PubMed: 11257905]
- Lynch WJ, Carroll ME. Sex differences in the acquisition of intravenously self-administered cocaine and heroin in rats. *Psychopharmacology*. 1999; 144(1):77–82. [PubMed: 10379627]
- Lynch WJ, Roth ME, Carroll ME. Biological basis of sex differences in drug abuse: preclinical and clinical studies. *Psychopharmacology*. 2002; 164(2):121–137. [PubMed: 12404074]
- Lynch WJ, Roth ME, Mickelberg JL, Carroll ME. Role of estrogen in the acquisition of intravenously self-administered cocaine in female rats. *Pharmacology, biochemistry, and behavior*. 2001; 68(4): 641–646.
- Madrigal JL, Olivenza R, Moro MA, Lizasoain I, Lorenzo P, Rodrigo J, Leza JC. Glutathione depletion, lipid peroxidation and mitochondrial dysfunction are induced by chronic stress in rat brain. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology*. 2001; 24(4):420–429. [PubMed: 11182537]
- Mahmoud R, Wainwright SR, Chaiton JA, Lieblich SE, Galea LA. Ovarian hormones, but not fluoxetine, impart resilience within a chronic unpredictable stress model in middle-aged female rats. *Neuropharmacology*. 2016; 107:278–293. [PubMed: 27018449]

- Manoli I, Alesci S, Blackman MR, Su YA, Rennert OM, Chrousos GP. Mitochondria as key components of the stress response. *Trends in endocrinology and metabolism: TEM*. 2007; 18(5): 190–198. [PubMed: 17500006]
- Mantsch JR, Baker DA, Funk D, Le AD, Shaham Y. Stress-Induced Reinstatement of Drug Seeking: 20 Years of Progress. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology*. 2016; 41(1):335–356. [PubMed: 25976297]
- Marchbanks RM, Ryan M, Day IN, Owen M, McGuffin P, Whatley SA. A mitochondrial DNA sequence variant associated with schizophrenia and oxidative stress. *Schizophrenia research*. 2003; 65(1):33–38. [PubMed: 14623372]
- Mattel MM, Klump K, Nigg JT, Breedlove SM, Sisk CL. Potential hormonal mechanisms of attention-deficit/hyperactivity disorder and major depressive disorder: a new perspective. *Hormones and behavior*. 2009; 55(4):465–479. [PubMed: 19265696]
- Martenyi F, Dossenbach M, Mraz K, Metcalfe S. Gender differences in the efficacy of fluoxetine and maprotiline in depressed patients: a double-blind trial of antidepressants with serotonergic or norepinephrinergic reuptake inhibition profile. *European neuropsychopharmacology: the journal of the European College of Neuropsychopharmacology*. 2001; 11(3):227–232. [PubMed: 11418283]
- Matuszewich L, Yamamoto BK. Effects of chronic stress on methamphetamine-induced dopamine depletions in the striatum. *Annals of the New York Academy of Sciences*. 2004; 1032:312–314. [PubMed: 15677439]
- Maurice T, Romieu P. Involvement of the sigma1 receptor in the appetitive effects of cocaine. *Pharmacopsychiatry*. 2004; 37(Suppl 3):S198–207. [PubMed: 15547786]
- Maurice T, Su TP. The pharmacology of sigma-1 receptors. *Pharmacology & therapeutics*. 2009; 124(2):195–206. [PubMed: 19619582]
- Meesters PD, de Haan L, Comijs HC, Stek ML, Smeets-Janssen MM, Weeda MR, Eikelenboom P, Smit JH, Beekman AT. Schizophrenia spectrum disorders in later life: prevalence and distribution of age at onset and sex in a dutch catchment area. *The American journal of geriatric psychiatry: official journal of the American Association for Geriatric Psychiatry*. 2012; 20(1):18–28. [PubMed: 22183010]
- Middaugh LD, Kelley BM. Operant ethanol reward in C57BL/6 mice: influence of gender and procedural variables. *Alcohol*. 1999; 17(3):185–194. [PubMed: 10231166]
- Middaugh LD, Kelley BM, Bandy AL, McGroarty KK. Ethanol consumption by C57BL/6 mice: influence of gender and procedural variables. *Alcohol*. 1999; 17(3):175–183. [PubMed: 10231165]
- Miller DB, Ali SF, O'Callaghan JP, Laws SC. The impact of gender and estrogen on striatal dopaminergic neurotoxicity. *Annals of the New York Academy of Sciences*. 1998; 844:153–165. [PubMed: 9668673]
- Moran-Santa Maria MM, McRae-Clark A, Baker NL, Ramakrishnan V, Brady KT. Yohimbine administration and cue-reactivity in cocaine-dependent individuals. *Psychopharmacology*. 2014; 231(21):4157–4165. [PubMed: 24710621]
- Morrison MF, Kallan MJ, Ten Have T, Katz I, Tweedy K, Battistini M. Lack of efficacy of estradiol for depression in postmenopausal women: a randomized, controlled trial. *Biological psychiatry*. 2004; 55(4):406–412. [PubMed: 14960294]
- Mulcrone J, Whatley SA, Ferrier IN, Marchbanks RM. A study of altered gene expression in frontal cortex from schizophrenic patients using differential screening. *Schizophrenia research*. 1995; 14(3):203–213. [PubMed: 7766531]
- Mutsaers HA, Tofighi R. Dexamethasone enhances oxidative stress-induced cell death in murine neural stem cells. *Neurotoxicity research*. 2012; 22(2):127–137. [PubMed: 22237944]
- Nakagawasai O, Oba A, Sato A, Arai Y, Mitazaki S, Onogi H, Wakui K, Nijima F, Tan-No K, Tadano T. Subchronic stress-induced depressive behavior in ovariectomized mice. *Life sciences*. 2009; 84(15–16):512–516. [PubMed: 19302813]
- National Institute of Health. Prescription Drug Abuse. National Institute on Drug Abuse; 2014. Research Report Series

- Natsvlishvili N, Gogvadze N, Zhuravliova E, Mikeladze D. Sigma-1 receptor directly interacts with Rac1-GTPase in the brain mitochondria. *BMC biochemistry*. 2015; 16:11. [PubMed: 25924612]
- Nilsen J, Brinton RD. Impact of progestins on estradiol potentiation of the glutamate calcium response. *Neuroreport*. 2002a; 13(6):825–830. [PubMed: 11997695]
- Nilsen J, Brinton RD. Impact of progestins on estrogen-induced neuroprotection: synergy by progesterone and 19-norprogesterone and antagonism by medroxyprogesterone acetate. *Endocrinology*. 2002b; 143(1):205–212. [PubMed: 11751611]
- Nilsen J, Diaz Brinton R. Mechanism of estrogen-mediated neuroprotection: regulation of mitochondrial calcium and Bcl-2 expression. *Proceedings of the National Academy of Sciences of the United States of America*. 2003; 100(5):2842–2847. [PubMed: 12604781]
- Okaro AC, Fennell DA, Corbo M, Davidson BR, Cotter FE. Pk11195, a mitochondrial benzodiazepine receptor antagonist, reduces apoptosis threshold in Bcl-X(L) and Mcl-1 expressing human cholangiocarcinoma cells. *Gut*. 2002; 51(4):556–561. [PubMed: 12235080]
- Olf M, Langeland W, Draijer N, Gersons BP. Gender differences in posttraumatic stress disorder. *Psychological bulletin*. 2007; 133(2):183–204. [PubMed: 17338596]
- Olsen RH, Johnson LA, Zuloaga DG, Limoli CL, Raber J. Enhanced hippocampus-dependent memory and reduced anxiety in mice over-expressing human catalase in mitochondria. *Journal of neurochemistry*. 2013; 125(2):303–313. [PubMed: 23383735]
- Pedersen WA, Wan R, Zhang P, Mattson MP. Urocortin, but not urocortin II, protects cultured hippocampal neurons from oxidative and excitotoxic cell death via corticotropin-releasing hormone receptor type I. *The Journal of neuroscience: the official journal of the Society for Neuroscience*. 2002; 22(2):404–412. [PubMed: 11784785]
- Pefanco MA, Kenny AM, Kaplan RF, Kuchel G, Walsh S, Kleppinger A, Prestwood K. The effect of 3-year treatment with 0.25 mg/day of micronized 17beta-estradiol on cognitive function in older postmenopausal women. *Journal of the American Geriatrics Society*. 2007; 55(3):426–431. [PubMed: 17341247]
- Pennell, S., Ellett, J., Rienick, C., Grimes, J. *Meth Matters: Report on Methamphetamine Users in Five Western Cities*. National Institute of Justice; 1999.
- Piano MR, Carrigan TM, Schwartz DW. Sex differences in ethanol liquid diet consumption in Sprague-Dawley rats. *Alcohol*. 2005; 35(2):113–118. [PubMed: 15963424]
- Piccinelli M, Wilkinson G. Gender differences in depression. Critical review. *The British journal of psychiatry: the journal of mental science*. 2000; 177:486–492. [PubMed: 11102321]
- Prendergast BJ, Onishi KG, Zucker I. Female mice liberated for inclusion in neuroscience and biomedical research. *Neuroscience and biobehavioral reviews*. 2014; 40:1–5. [PubMed: 24456941]
- Quinones-Jenab V, Ho A, Schlussman SD, Franck J, Kreek MJ. Estrous cycle differences in cocaine-induced stereotypic and locomotor behaviors in Fischer rats. *Behavioural brain research*. 1999; 101(1):15–20. [PubMed: 10342395]
- Quintanilla ME, Tampier L, Sapag A, Israel Y. Polymorphisms in the mitochondrial aldehyde dehydrogenase gene (Aldh2) determine peak blood acetaldehyde levels and voluntary ethanol consumption in rats. *Pharmacogenetics and genomics*. 2005a; 15(6):427–431. [PubMed: 15900217]
- Quintanilla ME, Tampier L, Valle-Prieto A, Sapag A, Israel Y. Complex I regulates mutant mitochondrial aldehyde dehydrogenase activity and voluntary ethanol consumption in rats. *FASEB journal: official publication of the Federation of American Societies for Experimental Biology*. 2005b; 19(1):36–42. [PubMed: 15629893]
- Quinton MS, Yamamoto BK. Neurotoxic effects of chronic restraint stress in the striatum of methamphetamine-exposed rats. *Psychopharmacology*. 2007; 193(3):341–350. [PubMed: 17458543]
- Rachman IM, Unerstall JR, Pfaff DW, Cohen RS. Estrogen alters behavior and forebrain c-fos expression in ovariectomized rats subjected to the forced swim test. *Proceedings of the National Academy of Sciences of the United States of America*. 1998; 95(23):13941–13946. [PubMed: 9811905]

- Radley J, Morilak D, Viau V, Campeau S. Chronic stress and brain plasticity: Mechanisms underlying adaptive and maladaptive changes and implications for stress-related CNS disorders. *Neuroscience and biobehavioral reviews*. 2015; 58:79–91. [PubMed: 26116544]
- Rammal H, Bouayed J, Younos C, Soulimani R. Evidence that oxidative stress is linked to anxiety-related behaviour in mice. *Brain, behavior, and immunity*. 2008; 22(8):1156–1159.
- Rappeneau V, Blaker A, Petro JR, Yamamoto BK, Shimamoto A. Disruption of the Glutamate-Glutamine Cycle Involving Astrocytes in an Animal Model of Depression for Males and Females. *Frontiers in behavioral neuroscience*. 2016; 10:231. [PubMed: 28018190]
- Rasgon NL, Dunkin J, Fairbanks L, Altshuler LL, Truong C, Elman S, Woolie TE, Brunhuber MV, Rapkin A. Estrogen and response to sertraline in postmenopausal women with major depressive disorder: a pilot study. *Journal of psychiatric research*. 2007; 41(3–4):338–343. [PubMed: 16697413]
- Raudensky J, Yamamoto BK. Effects of chronic unpredictable stress and methamphetamine on hippocampal glutamate function. *Brain research*. 2007a; 1135(1):129–135. [PubMed: 17198685]
- Raudensky J, Yamamoto BK. Effects of chronic unpredictable stress on monoamine transporter immunoreactivity and methamphetamine-induced dopamine release in the nucleus accumbens shell. *Synapse*. 2007b; 61(5):353–355. [PubMed: 17318887]
- Raut A, Iglewski M, Ratka A. Differential effects of impaired mitochondrial energy production on the function of mu and delta opioid receptors in neuronal SK-N-SH cells. *Neuroscience letters*. 2006; 404(1–2):242–246. [PubMed: 16808998]
- Raut A, Rao VR, Ratka A. Changes in opioid receptor proteins during mitochondrial impairment in differentiated SK-N-SH cells. *Neuroscience letters*. 2007; 422(3):187–192. [PubMed: 17611027]
- Recamier-Carballo S, Estrada-Camarena E, Reyes R, Fernandez-Guasti A. Synergistic effect of estradiol and fluoxetine in young adult and middle-aged female rats in two models of experimental depression. *Behavioural brain research*. 2012; 233(2):351–358. [PubMed: 22652396]
- Reichel CM, Bevins RA. Forced abstinence model of relapse to study pharmacological treatments of substance use disorder. *Current drug abuse reviews*. 2009; 2(2):184–194. [PubMed: 19630748]
- Reichel CM, Chan CH, Ghee SM, See RE. Sex differences in escalation of methamphetamine self-administration: cognitive and motivational consequences in rats. *Psychopharmacology*. 2012; 223(4):371–380. [PubMed: 22592902]
- Resnick SM, Espeland MA, An Y, Maki PM, Coker LH, Jackson R, Stefanick ML, Wallace R, Rapp SR, Women's Health Initiative Study of Cognitive Aging, I. Effects of conjugated equine estrogens on cognition and affect in postmenopausal women with prior hysterectomy. *The Journal of clinical endocrinology and metabolism*. 2009; 94(11):4152–4161. [PubMed: 19850684]
- Resnick SM, Maki PM, Rapp SR, Espeland MA, Brunner R, Coker LH, Granek IA, Hogan P, Ockene JK, Shumaker SA, Women's Health Initiative Study of Cognitive Aging, I. Effects of combination estrogen plus progestin hormone treatment on cognition and affect. *The Journal of clinical endocrinology and metabolism*. 2006; 91(5):1802–1810. [PubMed: 16522699]
- Rezin GT, Amboni G, Zugno AI, Quevedo J, Streck EL. Mitochondrial dysfunction and psychiatric disorders. *Neurochemical research*. 2009; 34(6):1021–1029. [PubMed: 18979198]
- Rezin GT, Cardoso MR, Goncalves CL, Scaini G, Fraga DB, Riegel RE, Comim CM, Quevedo J, Streck EL. Inhibition of mitochondrial respiratory chain in brain of rats subjected to an experimental model of depression. *Neurochemistry international*. 2008; 53(6–8):395–400. [PubMed: 18940214]
- Rice F, Harold GT, Boivin J, van den Bree M, Hay DF, Thapar A. The links between prenatal stress and offspring development and psychopathology: disentangling environmental and inherited influences. *Psychological medicine*. 2010; 40(2):335–345. [PubMed: 19476689]
- Rivier C, Vale W. Interaction of corticotropin-releasing factor and arginine vasopressin on adrenocorticotropin secretion in vivo. *Endocrinology*. 1983; 113(3):939–942. [PubMed: 6307672]

- Roberts DC, Bennett SA, Vickers GJ. The estrous cycle affects cocaine self-administration on a progressive ratio schedule in rats. *Psychopharmacology*. 1989; 98(3):408–411. [PubMed: 2501818]
- Rocca WA, Grossardt BR, Geda YE, Gostout BS, Bower JH, Maraganore DM, de Andrade M, Melton LJ 3rd. Long-term risk of depressive and anxiety symptoms after early bilateral oophorectomy. *Menopause*. 2008; 15(6):1050–1059. [PubMed: 18724263]
- Rocha BA, Fleischer R, Schaeffer JM, Rohrer SP, Hickey GJ. 17 Beta-estradiol-induced antidepressant-like effect in the forced swim test is absent in estrogen receptor-beta knockout (BERKO) mice. *Psychopharmacology*. 2005; 179(3):637–643. [PubMed: 15645223]
- Romano-Torres M, Fernandez-Guasti A. Estradiol valerate elicits antidepressant-like effects in middle-aged female rats under chronic mild stress. *Behavioural pharmacology*. 2010; 21(2):104–111. [PubMed: 20168212]
- Rondi-Reig L, Lemaigre Dubreuil Y, Martinou JC, Delhay-Bouchaud N, Caston J, Mariani J. Fear decrease in transgenic mice overexpressing bcl-2 in neurons. *Neuroreport*. 1997; 8(11):2429–2432. [PubMed: 9261803]
- Roth ME, Carroll ME. Sex differences in the escalation of intravenous cocaine intake following long- or short-access to cocaine self-administration. *Pharmacology, biochemistry, and behavior*. 2004; 78(2):199–207.
- Roubertoux PL, Sluyter F, Carlier M, Marcet B, Maarouf-Veray F, Cherif C, Marican C, Arrechi P, Godin F, Jamon M, Verrier B, Cohen-Salmon C. Mitochondrial DNA modifies cognition in interaction with the nuclear genome and age in mice. *Nature genetics*. 2003; 35(1):65–69. [PubMed: 12923532]
- Rubinow DR, Schmidt PJ. The neuroendocrinology of menstrual cycle mood disorders. *Annals of the New York Academy of Sciences*. 1995; 771:648–659. [PubMed: 8597438]
- Sabino V, Cottone P, Parylak SL, Steardo L, Zorrilla EP. Sigma-1 receptor knockout mice display a depressive-like phenotype. *Behavioural brain research*. 2009; 198(2):472–476. [PubMed: 19100292]
- Sadakerska-Chudy A, Kotarska A, Frankowska M, Jastrzebska J, Wydra K, Miszkiel J, Przegalinski E, Filip M. The Alterations in Mitochondrial DNA Copy Number and Nuclear-Encoded Mitochondrial Genes in Rat Brain Structures after Cocaine Self-Administration. *Molecular neurobiology*. 2016
- Sarnyai Z, Shaham Y, Heinrichs SC. The role of corticotropin-releasing factor in drug addiction. *Pharmacological reviews*. 2001; 53(2):209–243. [PubMed: 11356984]
- Schmidt PJ, Rubinow DR. Reproductive hormonal treatments for mood disorders in women. *Dialogues in clinical neuroscience*. 2002; 4(2):211–223. [PubMed: 22033644]
- Seeman MV. Treating schizophrenia at the time of menopause. *Maturitas*. 2012; 72(2):117–120. [PubMed: 22503514]
- Sepulveda J, Oliva P, Contreras E. Neurochemical changes of the extracellular concentrations of glutamate and aspartate in the nucleus accumbens of rats after chronic administration of morphine. *European journal of pharmacology*. 2004; 483(2–3):249–258. [PubMed: 14729114]
- Sepulveda MJ, Hernandez L, Rada P, Tucci S, Contreras E. Effect of precipitated withdrawal on extracellular glutamate and aspartate in the nucleus accumbens of chronically morphine-treated rats: an in vivo microdialysis study. *Pharmacology, biochemistry, and behavior*. 1998; 60(1):255–262.
- Sha S, Hong J, Qu WJ, Lu ZH, Li L, Yu WF, Chen L. Sex-related neurogenesis decrease in hippocampal dentate gyrus with depressive-like behaviors in sigma-1 receptor knockout mice. *European neuropsychopharmacology: the journal of the European College of Neuropsychopharmacology*. 2015; 25(8):1275–1286. [PubMed: 25983018]
- Shao L, Martin MV, Watson SJ, Schatzberg A, Akil H, Myers RM, Jones EG, Bunney WE, Vawter MP. Mitochondrial involvement in psychiatric disorders. *Annals of medicine*. 2008; 40(4):281–295. [PubMed: 18428021]
- Sherwin BB. The impact of different doses of estrogen and progestin on mood and sexual behavior in postmenopausal women. *The Journal of clinical endocrinology and metabolism*. 1991; 72(2):336–343. [PubMed: 1846872]

- Shimamoto A, Debold JF, Holly EN, Miczek KA. Blunted accumbal dopamine response to cocaine following chronic social stress in female rats: exploring a link between depression and drug abuse. *Psychopharmacology*. 2011; 218(1):271–279. [PubMed: 21638221]
- Simpkins JW, Yang SH, Sarkar SN, Pearce V. Estrogen actions on mitochondria-physiological and pathological implications. *Molecular and cellular endocrinology*. 2008; 290(1–2):51–59. [PubMed: 18571833]
- Sims NR, Anderson MF. Mitochondrial contributions to tissue damage in stroke. *Neurochemistry international*. 2002; 40(6):511–526. [PubMed: 11850108]
- Sparta DR, Ferraro FM 3rd, Fee JR, Knapp DJ, Breese GR, Thiele TE. The alcohol deprivation effect in C57BL/6J mice is observed using operant self-administration procedures and is modulated by CRF-1 receptor signaling. *Alcoholism, clinical and experimental research*. 2009; 33(1):31–42.
- Stefanova NA, Fursova A, Kolosova NG. Behavioral effects induced by mitochondria-targeted antioxidant SkQ1 in Wistar and senescence-accelerated OXYS rats. *Journal of Alzheimer's disease: JAD*. 2010; 21(2):479–491.
- Su TP, Hayashi T, Maurice T, Buch S, Ruoho AE. The sigma-1 receptor chaperone as an inter-organelle signaling modulator. *Trends in pharmacological sciences*. 2010; 31(12):557–566. [PubMed: 20869780]
- Su YA, Wu J, Zhang L, Zhang Q, Su DM, He P, Wang BD, Li H, Webster MJ, Traumatic Stress Brain Study, G. Rennert OM, Ursano RJ. Dysregulated mitochondrial genes and networks with drug targets in postmortem brain of patients with posttraumatic stress disorder (PTSD) revealed by human mitochondria-focused cDNA microarrays. *International journal of biological sciences*. 2008; 4(4):223–235. [PubMed: 18690294]
- Sutton RE, Koob GF, Le Moal M, Rivier J, Vale W. Corticotropin releasing factor produces behavioural activation in rats. *Nature*. 1982; 297(5864):331–333. [PubMed: 6978997]
- Tata DA, Yamamoto BK. Chronic stress enhances methamphetamine-induced extracellular glutamate and excitotoxicity in the rat striatum. *Synapse*. 2008; 62(5):325–336. [PubMed: 18288648]
- Taylor J, Harris N, Vogel WH. Voluntary alcohol and cocaine consumption in “low” and “high” stress plasma catecholamine responding rats. *Pharmacology, biochemistry, and behavior*. 1990; 37(2):359–363.
- Thase ME, Entsuah R, Cantillon M, Kornstein SG. Relative antidepressant efficacy of venlafaxine and SSRIs: sex-age interactions. *Journal of women's health*. 2005; 14(7):609–616.
- S.N.E.X., editor. United Nations Office on Drugs and Crime. World Drug Report in: United Nations publication. 2014.
- Urani A, Roman FJ, Phan VL, Su TP, Maurice T. The antidepressant-like effect induced by sigma(1)-receptor agonists and neuroactive steroids in mice submitted to the forced swimming test. *The Journal of pharmacology and experimental therapeutics*. 2001; 298(3):1269–1279. [PubMed: 11504830]
- Valdez GR, Roberts AJ, Chan K, Davis H, Brennan M, Zorrilla EP, Koob GF. Increased ethanol self-administration and anxiety-like behavior during acute ethanol withdrawal and protracted abstinence: regulation by corticotropin-releasing factor. *Alcoholism, clinical and experimental research*. 2002; 26(10):1494–1501.
- Vale W, Spiess J, Rivier C, Rivier J. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. *Science*. 1981; 213(4514):1394–1397. [PubMed: 6267699]
- Valenza M, DiLeo A, Steardo L, Cottone P, Sabino V. Ethanol-related behaviors in mice lacking the sigma-1 receptor. *Behavioural brain research*. 2016; 297:196–203. [PubMed: 26462569]
- van Haaren F, Anderson K. Sex differences in schedule-induced alcohol consumption. *Alcohol*. 1994; 11(1):35–40. [PubMed: 8142066]
- Varga ZV, Ferdinandy P, Liaudet L, Pacher P. Drug-induced mitochondrial dysfunction and cardiotoxicity. *American journal of physiology Heart and circulatory physiology*. 2015; 309(9):H1453–1467. [PubMed: 26386112]
- Videbech P. PET measurements of brain glucose metabolism and blood flow in major depressive disorder: a critical review. *Acta psychiatrica Scandinavica*. 2000; 101(1):11–20. [PubMed: 10674946]

- Vitcheva V, Simeonova R, Kondeva-Burdina M, Mitcheva M. Selective Nitric Oxide Synthase Inhibitor 7-Nitroindazole Protects against Cocaine-Induced Oxidative Stress in Rat Brain. *Oxidative medicine and cellular longevity*. 2015; 2015:157876. [PubMed: 26576217]
- Walf AA, Frye CA. A review and update of mechanisms of estrogen in the hippocampus and amygdala for anxiety and depression behavior. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology*. 2006; 31(6):1097–1111. [PubMed: 16554740]
- Walf AA, Paris JJ, Frye CA. Chronic estradiol replacement to aged female rats reduces anxiety-like and depression-like behavior and enhances cognitive performance. *Psychoneuroendocrinology*. 2009; 34(6):909–916. [PubMed: 19216030]
- Walf AA, Rhodes ME, Frye CA. Antidepressant effects of ERbeta-selective estrogen receptor modulators in the forced swim test. *Pharmacology, biochemistry, and behavior*. 2004; 78(3):523–529.
- Wang X. The expanding role of mitochondria in apoptosis. *Genes & development*. 2001; 15(22):2922–2933. [PubMed: 11711427]
- Wang X, Simpkins JW, Dykens JA, Cammarata PR. Oxidative damage to human lens epithelial cells in culture: estrogen protection of mitochondrial potential, ATP, and cell viability. *Investigative ophthalmology & visual science*. 2003; 44(5):2067–2075. [PubMed: 12714645]
- Weeber EJ, Levy M, Sampson MJ, Anflous K, Armstrong DL, Brown SE, Sweatt JD, Craigen WJ. The role of mitochondrial porins and the permeability transition pore in learning and synaptic plasticity. *The Journal of biological chemistry*. 2002; 277(21):18891–18897. [PubMed: 11907043]
- Weinberg SE, Chandel NS. Targeting mitochondria metabolism for cancer therapy. *Nature chemical biology*. 2015; 11(1):9–15. [PubMed: 25517383]
- Welton AJ, Vickers MR, Kim J, Ford D, Lawton BA, MacLennan AH, Meredith SK, Martin J, Meade TW, team, W. Health related quality of life after combined hormone replacement therapy: randomised controlled trial. *Bmj*. 2008; 337:a1190. [PubMed: 18719013]
- Wittchen HU, Hoyer J. Generalized anxiety disorder: nature and course. *The Journal of clinical psychiatry*. 2001; 62(Suppl 11):15–19. discussion 20–11.
- World Health Organization. Gender disparities in mental health. 2016.
- Wu HB, Niyomchai T, Festa E, Minerly AE, Weierstall K, Hunter D, Sun W, Weiner J, Jenab S, Quinones-Jenab V. Effects of RU 486 and tamoxifen on cocaine-induced behavioral and endocrinologic activations in male and female Fischer rats. *Ethnicity & disease*. 2008; 18(2 Suppl 2):S2-81–86.
- Xing G, Barry ES, Benford B, Grunberg NE, Li H, Watson WD, Sharma P. Impact of repeated stress on traumatic brain injury-induced mitochondrial electron transport chain expression and behavioral responses in rats. *Frontiers in neurology*. 2013a; 4:196. [PubMed: 24376434]
- Yang SH, Liu R, Perez EJ, Wen Y, Stevens SM Jr, Valencia T, Brun-Zinkernagel AM, Prokai L, Will Y, Dykens J, Koulen P, Simpkins JW. Mitochondrial localization of estrogen receptor beta. *Proceedings of the National Academy of Sciences of the United States of America*. 2004; 101(12):4130–4135. [PubMed: 15024130]
- Zheng J, Ramirez VD. Rapid inhibition of rat brain mitochondrial proton F0F1-ATPase activity by estrogens: comparison with Na⁺, K⁺ -ATPase of porcine cortex. *European journal of pharmacology*. 1999; 368(1):95–102. [PubMed: 10096774]
- Zorrilla EP, Logrip ML, Koob GF. Corticotropin releasing factor: a key role in the neurobiology of addiction. *Frontiers in neuroendocrinology*. 2014; 35(2):234–244. [PubMed: 24456850]
- Zorrilla EP, Valdez GR, Weiss F. Changes in levels of regional CRF-like-immunoreactivity and plasma corticosterone during protracted drug withdrawal in dependent rats. *Psychopharmacology*. 2001; 158(4):374–381. [PubMed: 11797058]

Figure 1

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 (ERP). 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.