Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Sex/Gender Differences in The Time-Course for the Development of Substance Use Disorder: A Focus on the Telescoping Effect

Eleanor Blair Towers[1, 2], Ivy L. Williams[1], Emaan I. Qillawala[1], Emilie F. Rissman[3], Wendy J. Lynch[1*]

[1]Psychiatry and Neurobehavioral Sciences, University of Virginia, Charlottesville, VA

[2]Medical Scientist Training Program, University of Virginia, Charlottesville, VA

[3]Center for Human Health and the Environment and Program in Genetics, North Carolina State University, Raleigh, NC

Running Title: Sex Differences in the Progression to Addiction

***Correspondence Author:** Wendy J. Lynch, PhD, e-mail: wlynch@virginia.edu, address: 450 Ray C. Hunt Drive Charlottesville, VA 22903

Total number of pages (60)
Number of tables (2)
Number of figures (1)
Number of references (402)
Number of words in abstract (225)

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AUD, alcohol use disorder; CaUD, cannabis use disorder; CoUD, cocaine use disorder; Bdnf-IV, brain-derived neurotrophic factor exon IV promoter; CB_1 receptor, cannabinoid receptor type 1; CP, Ca2+-permeable; D1 receptor, dopamine receptor D1 and D5; D2 receptor, dopamine receptor D2, D3, D4; DA, dopamine; dmPFC, dorsal medial prefrontal cortex; GLT-1, Na+-dependent glial glutamate transporter; Grin1, glutamate ionotropic receptor NMDA type subunit 1; Grin2a, glutamate ionotropic receptor NMDA type subunit 2a; Grin2b, glutamate ionotropic receptor NMDA type subunit 2b; LH, luteinizing hormone; FCG, four core genotype; FSH, follicle stimulating hormone; mGlu, metabotropic glutamate receptor; MPEP, 2-methyl-6-(phenylethynyl)pyridine); mPFC, medial prefrontal cortex; NAc, nucleus accumbens; NMDA, N-methyl-D-aspartate; PET, positron emission tomography; OUD, opioid use disorder; OVX, ovariectomized; PFC, prefrontal cortex; SUD, substance use disorder; TUD, tobacco use disorder; VTA, ventral tegmental area

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Abstract

Sex/gender effects have been demonstrated for multiple aspects of addiction, with one of the most commonly cited examples being the "telescoping effect" where women meet criteria and/or seek treatment for substance use disorder (SUD) after fewer years of drug use as compared to men. This phenomenon has been reported for multiple drug classes including opioids, psychostimulants, alcohol, and cannabis, as well as non-pharmacological addictions, such as gambling. However, there are some inconsistent reports that show either no difference between men and women or opposite effects and a faster course to addiction in men than women. Thus, the goals of this review are to evaluate evidence for and against the telescoping effect in women and to determine the conditions/populations for which the telescoping effect is most relevant. We also discuss evidence from preclinical studies which strongly support the validity of the telescoping effect and show that female animals develop addiction-like features (e.g., compulsive drug use, an enhanced motivation for the drug and, enhanced drug-craving/vulnerability to relapse) more readily than male animals. We also discuss biological factors that may contribute to the telescoping effect, such as ovarian hormones, and its neurobiological basis focusing on the mesolimbic dopamine reward pathway and the corticomesolimbic glutamatergic pathway considering the critical roles these pathways play in the rewarding/reinforcing effects of addictive drugs and SUD. We conclude with future research directions, including intervention strategies to prevent the development of SUD in women.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Significance Statement

One of the most widely cited gender/sex differences in substance use disorder (SUD) is "the telescoping effect" which reflects an accelerated course in women versus men for the development and/or seeking treatment for SUD. This review evaluates evidence for and against a telescoping effect drawing upon data from both clinical and preclinical studies. We also discuss the contribution of biological factors and underlying neurobiological mechanisms and highlight potential targets to prevent the development of SUD in women.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Table of Contents:

1. Introduction
2. Sex Differences in The Progression to Addiction
    - 2.1 Evidence for and Against a Telescoping Effect in Women
    - 2.2 Sex Differences in Animal Models of Initial Vulnerability to Substance Use
    - 2.3 Sex Differences in Animal Models of SUD
    - 2.3 Summary and Integration of Preclinical and Clinical Findings
3. Biological Factors
    - 3.1 Ovarian Hormones
        - 3.1.1 Human Studies- Ovarian Hormones and Substance Use
        - 3.1.2 Human Studies- Ovarian Hormones and SUD
        - 3.1.3 Animal Studies- Ovarian Hormones and Substance Use
        - 3.1.4 Animal Studies- Ovarian Hormones and SUD
    - 3.2 Sex Chromosomes
        - 3.2.1 Animal Studies- Sex Chromosomes and Substance Use
        - 3.2.1 Animal Studies- Sex Chromosomes and SUD
    - 3.3 Summary and Integration of Preclinical and Clinical Findings
4. Neurobiological Mechanisms
    - 4.1 Mesolimbic Dopamine
        - 4.1.1 Human Studies- Dopamine and Substance Use
        - 4.1.2 Human Studies- Dopamine and SUD
        - 4.1.3 Animal Studies- Dopamine and Substance Use
        - 4.1.4 Animal Studies- Dopamine and SUD
    - 4.2 Corticomesolimbic Glutamate
        - 4.2.1 Human Studies- Glutamate and Substance Use
        - 4.2.2 Human Studies- Glutamate and SUD
        - 4.2.3 Animal Studies- Glutamate and Substance Use
        - 4.2.4 Animal Studies- Glutamate and SUD
    - 4.3 Summary and Integration of Preclinical and Clinical Findings
5. Conclusions and Future Research Directions

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

1. Introduction

Despite higher rates of drug use and substance use disorder (SUD) in men, women are more vulnerable than men on many aspects of the disease. One striking example is "the telescoping effect" which reflects an accelerated course in women versus men for the transition from initiation of substance use to meeting criteria for SUD and/or seeking treatment for SUD. This phenomenon was originally described for alcohol more than 30 years ago (Ashley et al. 1977; Hesselbrock et al. 1985; Piazza et al. 1989) and the observation has been replicated in multiple subsequent studies with alcohol (Diehl et al. 2007; Johnson et al. 2005; Randall et al. 1999; Lewis and Nixon, 2014; Hesselbrock et al. 1985; Piazza et al. 1989; Mann et al. 1992, 2005; McCance-Katz et al. 1999; Hernandez-Avilaet al. 2004) as well as with other drug classes, including stimulants (e.g., cocaine, nicotine/tobacco, methamphetamine; McCance-Katz et al. 1999; Griffin et al. 1989; White et al. 1996; Brecht et al. 2004; Sofuoglu et al. 1999; Thorner et al. 2007; O'Brien and Anthony, 2005; Haas and Peters, 2000), opioids (Hernandez-Alvila et al. 2004; Lewis et al. 2014; Peltier et al. 2021; Anglin et al. 1987; Adelson et al. 2018; Hser et al. 1987; Back et al. 2011; DiFranza et al. 2002), and cannabis (Hernandez-Avila et al. 2004; Lewis et al. 2014; Khan et al. 2013; Ehlers et al. 2010; Haas and Peters, 2000). It has also been reported for non-pharmacological addictions, such as gambling (Tavares et al. 2003; Ladd and Petry, 2002; Ibanez et al. 2003; Grant et al. 2012).

The telescoping effect in women has been widely noted in studies of SUD yet there are some inconsistent reports that show either no difference between men and women in the time-course for the development of SUD (Alvanzo et al. 2011; Stoltman et al. 2015; DiFranza et al. 2007) or the reverse, a faster course in men than women (Keyes et al. 2010; Slutske et al. 2015). Changes in sociocultural factors, such as a progressive destigmatization of drug use in women over time,

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

have been proposed to account for differences observed between women and men in the original telescoping studies versus more recent ones (Nicolaides, 1996). Recent studies, using population-based surveys, may be further confusing the literature since sex/gender differences in the time-course for the development of SUD are confounded by differences in the likelihood of developing SUD and seeking treatment for SUD, both of which are greater in men than women (Wagner and Anthony, 2007; Greenfield, 2007). Some notable exceptions are for psychotherapeutics (i.e., non-medical use of pain relievers, sedatives, stimulants, and tranquilizers) and tobacco; in these cases, women are more likely than men to develop a SUD (Cotto et al. 2010; Lopez-Quintero et al. 2011). The telescoping effect has also been replicated in several studies conducted during the past ten years (Lewis and Nixon, 2014; Lewis et al. 2014; Grant et al. 2012; Peltier et al. 2021; Khan et al. 2013; Sylvestre et al. 2018), with robust effects within treatment seeking populations (e.g. Randall et al. 1999; Hernandez-Avila et al. 2004; Ibanez et al. 2003). The validity of the telescoping effect is also strongly supported by results from preclinical studies which show that, like the human situation, female animals develop addiction-like features more readily than male animals (Kerstetter et al. 2012; Perry et al. 2013, 2015; Kawa and Robinson, 2019; Lynch and Taylor, 2004; Towers et al. 2021).

Thus, the purpose of this review is to evaluate evidence for and against the telescoping effect in women and determine the conditions/populations for which the telescoping effect is most relevant. We also discuss preclinical findings of sex differences in order to establish a biological basis for the telescoping effect. This evidence is divided into findings from *animal models of substance use* (see **Table 1** for a glossary of terms), which generally use short-access drug self-administration (1-2 hr/day) and focus on differences in the acquisition of drug self-administration or maintenance levels of intake or motivation for the drug, versus *animal models of SUD*, which

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

typically use extended-access drug self-administration (≥ 6 hr/day) and focus on differences in the development and/or expression of addiction-like features like those observed in humans with a SUD (e.g., escalation of drug use, compulsive drug use despite punishment, an enhanced motivation for the drug, enhanced drug-craving/vulnerability to relapse). Mechanisms underlying the telescoping effect are also explored, including the potential for ovarian hormones to drive an enhanced vulnerability in women and female laboratory animals during both initial substance use and with the development of SUD. We also discuss neurobiological mechanisms of substance use and SUD in women and men and male and female laboratory animals focusing on the mesolimbic dopamine reward pathway and corticomesolimbic glutamatergic pathways considering the critical roles these pathways play in the rewarding/reinforcing effects of addictive drugs and SUD. The potential role of sex chromosomes and other signaling pathways, including the potential for stress and the HPA-axis to enhance vulnerability in females, are also briefly discussed. We conclude with implications for sex-specific interventions for SUD and future research directions.

Human studies were selected based on Pub Med and Google Scholar searches using the key words telescoping, time-course, trajectory, alcohol, cocaine, methamphetamine, opioids, fentanyl, heroin, morphine, oxycodone, cannabis, smoking, nicotine, tobacco, illicit drug use, initiation of use, regular use, problem use, addiction, and SUD. Preclinical studies were identified using these terms as well as acquisition, reinforcing effects, self-administration, addiction phenotype, relapse, enhanced motivation, compulsive use, escalation, binge intake, and extended-access self-administration. Human and animal studies of biological factors and neurobiological mechanisms focused on these terms as well as ovarian hormones, estrous cycle, menstrual cycle, luteal, follicular, estradiol, progesterone, dopamine, glutamate, excitability,

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

nucleus accumbens (NAc), ventral tegmental area (VTA), medial prefrontal cortex (mPFC). Throughout this review, the term *sex* refers to biological differences between women and men and male and female laboratory animals related to sex hormones, chromosomes, gene expression, anatomy, or physiology (Committee on Understanding the Biology of Sex and Gender Differences, 2001). The term *gender* refers to socially determined differences between women and men roles that vary over time and between cultures (Committee on Understanding the Biology of Sex and Gender Differences, 2001).

2. Sex Differences in The Progression to Addiction

2.1 Evidence for and Against a Telescoping Effect in Women

The original reports of a telescoping effect were based on self-reports and structured interviews from men and women with an alcohol use disorder (AUD; i.e., abuse or dependence based on DSM-III/IV) detailing the time-line of onset of major alcohol-related life events. These events include first drink, first intoxication, continuous consumption, onset of dependence, and first inpatient treatment which have been shown to occur in a chronological sequence with a high level of predictability in both women and men (Schuckit et al. 1995). Using this framework, these studies consistently show that women progress more rapidly from regular alcohol use to developing problematic alcohol use or an AUD (**Table 2 a-b;** Diehl et al. 2007; Johnson et al. 2005; Randall et al. 1999; Hesselbrock et al. 1985). Women also have a shorter course from the onset of problematic use/AUD to seeking treatment for the disorder than men (Lewis and Nixon, 2014; Piazza et al. 1989; Randall et al. 1999; Diehl et al. 2007; Hernandez-Avila et al. 2004; Man et al. 1992, 2005; Ashley et al. 1977; McCance-Katz et al. 1999). This faster progression to treatment seeking may be attributable to an earlier onset of severe SUD (5 or more DSM-V

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

symptoms) considering that at treatment entry, women have more severe clinical profiles than men (e.g., more medical, psychological, behavioral, and social problems; Greenfield et al. 2010). This conclusion is further supported by studies showing that women have an accelerated course and/or an enhanced sensitivity to alcohol-related health consequences as compared to men. Some of the differences in health decline include a faster course in women than men for the development of alcohol-associated cirrhosis (Loft et al. 1987) and brain atrophy (Hommer et al. 1996; Hommer et al. 2001; Mann et al. 1992; Mann et al. 2005), as well as greater alcohol-associated effects on cardiac and skeletal muscle in women than men (Fernandez-Sola et al. 1997; Urbano-Marquez et al. 1995).

Similar methods have been used to establish sex/gender differences in transitions from initial use to regular use, problematic use, and SUD and/or treatment for SUD with other addictive drugs, including opioids, psychostimulants, cannabis, and tobacco (**Table 2 a-b**). These studies show that compared to men, women have a shorter duration of opioid (Aldelson et al. 2018; Hernandez-Avila et al. 2004; Hser 1987; Peltier et al. 2021), psychostimulants (cocaine and methamphetamine; Brecht et al. 2004; Griffin et al. 1989; Haas and Peters, 2000; McCance-Katz et al. 1999; O'Brien and Anthony, 2005; Sofuoglu et al. 1999; White et al. 1996), and cannabis use (Hernandez-Avila et al. 2004) prior to entering treatment and a faster progression from initial use of opioids (Back et al. 2011; Anglin et al. 1987; Lewis et al. 2014), cocaine (White et al. 1996; Sofuoglu et al. 1999; O'Brien and Anthony, 2005), tobacco (DiFranza et al. 2002; Sylvestre et al. 2018; Scragg et al. 2008; Thorner et al. 2007), and cannabis (Ehlers et al. 2010; Khan et al. 2013; Lewis et al. 2014) to regular or problem use. The same pattern has also been reported for gambling wherein women show a faster progression from the initiation of gambling to developing a problem with gambling or to meeting criteria for pathological gambling

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

compared to men (Ladd and Petry, 2002; Ibáñez et al. 2003; Tavares et al. 2003; Grant et al. 2012). As with findings with alcohol, women with SUD have more severe clinical profiles than men with SUD at treatment entry (Arfken et al. 2001; Fernandez-Montalvo et al. 2014), and show an accelerated course and/or enhanced vulnerability to drug-related medical consequences including a greater risk of infectious diseases with opioid use (i.e, hepatitis C; Iversen et al. 2010 and AIDS; Des Jarlaise et al. 2012), an earlier age for onset of psychotic disorders with cannabis use (Large et al. 2011), overall greater risk for cocaine-induced death (de la Fuente et al. 2014), shorter time interval between onset of cocaine use and its fatal outcome (Origer et al. 2014; see Agabio et al. 2016 for review), and increased susceptibility to smoking-associated lung cancer (Hansen et al. 2018; Kiyohara et al. 2010).

However, not all studies have observed a telescoping effect in women (Alvanzo et al. 2011; DiFranza et al. 2007) and findings from non-treatment seeking populations, particularly population-based studies, have been mixed (**Table 2 b**; e.g., Ehlers et al. 2010; Keyes et al. 2010; Khan et al. 2013; Slutske et al. 2015; Stoltman et al. 2015; Back et al. 2011). Probably the most controversial findings are from the Keyes et al. (2010) study which was a large-scale study of alcohol use trajectories based on population-level data from two US national surveys (conducted in 1991-1992 and 2001-2002) of five birth cohorts (1934-1943, 1944-1953, 1954-1963, 1964-1973, and 1974-1983). They analyzed survival probabilities over time for the transition from initial alcohol use to developing an AUD and from the onset of an AUD to seeking treatment for the disorder. In contrast to predicted effects, men transitioned faster than women from initial alcohol use to AUD and from developing AUD to seeking treatment for the disorder. However, another interpretation is that the data reflect a greater risk in men for developing an AUD and a lower likelihood in women of seeking treatment for AUD. Indeed, the analysis of alcohol use

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

trajectories in the individuals that actually developed an AUD are consistent with previous reports of a telescoping effect. In addition, the mean number of years between initial alcohol use and the development of AUD was shorter in women than men (i.e., alcohol dependence as defined by the DSM-IV; 3.7 years versus 4.2 years). Similarly, when the analysis was limited to individuals that sought treatment for an AUD, women had fewer years between the onset of an AUD to seeking treatment for the disorder (6.1 versus 7 years). These differences were modest, however, particularly for the time-course for developing an AUD, and the effect was limited to one of the five birth cohorts (cohort 2). The effect for treatment was statistically significant when data were collapsed across all the cohorts, but analysis within each cohort only yielded significance for cohort 5 (19.4 versus 23.5).

These data, together with mixed reports of a telescoping effect in non-treatment seeking populations (Stoltman et al. 2015; Back et al. 2011), indicate that the telescoping effect may be most relevant within treatment-seeking populations, which presumably include only individuals that develop a severe SUD requiring treatment. This idea is also consistent with findings from a population-level study showing that adolescent and young adult females are less likely than their male counterparts to have a mild to moderate illicit drug use disorder (other than cannabis), but equally likely, if not more likely, to have a severe illicit drug use disorder (i.e., classified as dependence according to DSM-IV; Cotto et al. 2010). It is also supported by population-level data (Wave I and II of the National Epidemiologic Survey on Alcohol and Related Conditions) showing that women with a history childhood maltreatment, which is known to be associated with greater addiction severity (see Puetz and McCrory, 2015 for review), had a faster progression from the onset of drinking to developing an AUD than women without childhood maltreatment and men with and without this history (Schuckher et al. 2018). Importantly, this

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

vulnerable in-treatment population is the population that needs to be studied for insights into prevention and treatment.

While the mechanisms underlying the telescoping effect are not yet known, it is likely that both sociocultural-gender differences and biological-sex differences contribute. For example, gender differences in the use of the health care system have been suggested as a potential explanation for the telescoping effect since women seek care sooner after initiating substance use or developing a SUD disorder than men. Social stigma against substance use and SUD in women may also cause women to seek treatment earlier after initiating substance use and/or developing a SUD than men. This does not appear to be the case, however, since in contrast to the gender difference for seeking medical care overall, women are not more likely than men to seek treatment for a SUD (Greenfield et al. 2007; Center for Behavioral Health Statistics and Quality, 2015). Women are also more likely than men to be primary caregivers, and fear of losing custody of children is commonly reported as a barrier to seeking care for SUD (Pool et al. 2001; Mackay et al. 2020). Greater socio-relational impairment in women than men has also been reported to serve as a barrier to seeking treatment for a SUD in women. These gender differences may explain the disparity in SUD treatment between men and women and further support the conclusion that women who enter SUD treatment represent a vulnerable population that develops a severe SUD. This explanation also fits the data indicating that at the start of treatment for SUD, women have more severe SUDs and have more psychiatric and medical comorbidities than men. Biological factors also likely contribute to this vulnerability in women and the telescoping effect considering that similar behavior has been reported in female versus male laboratory animals (as detailed below).

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

2.2 Sex Differences in Animal Models of Initial Vulnerability to Substance Use

Preclinical studies of sex differences in addiction have focused predominately on vulnerability during early phases of the addiction process, such as acquisition of drug self-administration under short access conditions. These differences are ideally studied under low drug doses which maximize individual differences; low doses are also less likely than high doses to induce negative side-effects that may counter the reinforcing effects of the drug or impact the animal's ability to respond (Lynch et al. 2010). Results from studies comparing male and female rats have consistently revealed faster rates of acquisition and greater percent group acquisition in females than males under low dose conditions (e.g., Carroll et al. 2002; Lynch, 2008; Roth and Carroll, 2004). While most of this work has focused on cocaine, similar findings have been reported for other classes of drugs including opioids, alcohol, and cannabis, and for other psychostimulants such as nicotine and methamphetamine (for reviews see Becker and Hu, 2008; Lynch, 2006; Carroll et al. 2004). Females also typically self-administer more drug under short-access conditions (fixed-ratio 1, 1-2-hr/day) than males (e.g., Smith et al. 2021; Roberts et al. 1989), but this measure is less sensitive to individual differences and sex differences are not always observed (e.g., Towers et al. 2019; Roth and Carroll, 2004). The direction of effects can also be difficult to interpret from maintenance levels of intake since lower intake may reflect less sensitivity to the reinforcing effects of the drug (e.g., the dose may function as a reinforcer in only a subset of the animals) or greater sensitivity (e.g., less drug is needed to maintain a preferred level of effect). Motivation to obtain the drug, as assessed under progressive-ratio schedules or the threshold procedure, is sensitive to individual differences and is a linear measure of reinforcing effects (i.e., larger doses maintain higher levels of responding). Numerous studies have shown that females are more motivated to obtain infusions of addictive

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

drugs, and this effect has been observed at both low and high drug doses and for multiple addictive drugs (e.g., Mello et al. 2007; Roth and Carroll, 2004; for review see Lynch 2006; 2018). These findings indicate that females have an enhanced sensitivity to reinforcing effects of addictive drugs (**Figure 1**).

2.3 Sex Differences in Animal Models of SUD

Much less is known regarding sex differences in vulnerability during later stages of the addiction process, and more specifically, following the development of an addiction-like phenotype. The use of extended-access drug self-administration appears to be critical to inducing this phenotype which has been defined by the development of one of more key addiction-like features, such as escalation of drug intake over time, binge/abstinence patterns of drug use, compulsive drug use despite negative consequences, the development of physical dependence, an increased preference for the drug over a non-drug reward, an enhanced motivation to obtain the drug, and enhanced drug-craving/vulnerability to relapse (Lynch 2018). While no one procedure captures all 11 diagnostic criteria listed in the DSM-5 (American Psychiatric Association, 2013), there are multiple extended-access procedures that induce two or more of these clinical features, the threshold for a diagnosis of SUD in humans. For example, with the most commonly used extended-access procedure, the long-access procedure (Ahmed and Koob, 1998), animals have unrestricted, fixed-ratio-1 access to infusions of a drug, such as cocaine, heroin, fentanyl, nicotine, methamphetamine, for 6-12 hours/day. Under these conditions, animals self-administer high levels of the drug and show an escalating pattern of use over time, which is believed to mimic the excessive drug use and loss of control features of SUD in humans. This loss of control feature is also observed in rats given extended-, intermittent-access to a drug using either a

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

discrete trial (Fitch and Roberts, 1993) or a fixed-ratio 1 procedure (Zimmer et al. 2012), which results in a binge-abstinent of pattern of drug self-administration characterized by cycles of heavy/prolonged periods of drug use (binge intake) separated by periods of self-imposed abstinence. For example, rats given 24-hr/day intermittent-access to cocaine, heroin, or speedball using a discrete trial procedure (4, 10 min trials/hr), self-administer high levels of the drug in binge-abstinent patterns that are dysregulated from the normal diurnal cycle (i.e., responding occurs at high levels throughout the light-dark phase). Similar binge-abstinent patterns have been observed for cocaine and fentanyl under extended, intermittent-access conditions (2 5-min trials/hr) using a fixed-ratio 1 schedule.

Notably, extended-access drug self-administration using the long-access procedure or an intermittent-access procedure leads to the development of other core characteristics of SUD including compulsive drug use, as assessed by continued drug use despite punishment (e.g., foot shock), an enhanced motivation to use the drug, as assessed using a progressive-ratio schedule or a threshold procedure, and enhanced drug-craving/vulnerability to relapse, as assessed using an extinction/reinstatement procedure (Ahmed and Koob, 1998; Allain et al. 2015; Balster and Woolverton, 1982; Fitch and Roberts, 1993; Lynch and Carroll, 2001; Lynch, 2018). Expression of each of these features emerges over abstinence following extended-access self-administration and increases, rather than decreases, in magnitude over time. This “incubation” effect is robust and has been described for cue-induced drug-craving in humans for nicotine (Bedi et al. 2011), methamphetamine (Wang et al. 2013), cocaine (Wang et al. 2013), and alcohol (Li et al. 2014; Bach et al. 2019) and in animals for these drugs along with opioids (see Pickens et al. 2011 and Li et al. 2015 for reviews). A similar incubation effect has also been reported for the expression of enhanced motivation with cocaine (Towers et al. 2021) and for compulsive use with cocaine

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

and heroin (Towers et al. 2021; Gancarz-Kausch et al. 2014). Notably, as with humans, the development of some of these addiction-like features (e.g., an enhanced motivation for the drug) are expressed long-term and appear to reflect a relatively permanent shift to a higher motivational state (see Lynch et al. 2021). While it is possible to induce these addiction-like features using short-access drug self-administration procedures, it occurs in only a small minority of the rats (~30%; Belin and Deroche-Gamonet, 2012). The phenotype is also more robust following extended- versus short-access self-administration (e.g. Fischer et al. 2013; Pacchioni et al. 2011). Evidence also shows that molecular changes differ following extended- versus short-access self-administration.

Sex differences have been reported for both extended-access self-administration and the induction of an addiction-like phenotype following extended-access self-administration and abstinence (see **Figure 1**). During extended-access self-administration, studies have shown that female rodents self-administer higher levels of drugs including alcohol, opioids, such as heroin, fentanyl, oxycodone, and morphine, and psychostimulants, such as cocaine, methamphetamine, and nicotine, compared to male rodents (Becker and Koob, 2016; Carroll et al. 2005; George et al. 2021; Kawa and Robinson, 2019; Lynch and Taylor, 2004, 2005; Moore and Lynch, 2015; Nicolas et al. 2019; Reichel et al. 2012; Roth and Carroll, 2004; Sanchez et al. 2014; Smith et al. 2011; Towers et al. 2019; 2022). Female non-human primates also self-administer more phencyclidine than male non-human primates under long-access conditions (Carroll et al. 2005). Sex differences in intake are most apparent under low dose conditions and in procedures that do not limit total hourly or daily intake as such procedures increase the likelihood of individual differences. There are also sex differences in patterns of extended-access drug self-administration under both high and low dose conditions with female rats and mice showing

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

greater escalation of alcohol, opioids, and psychostimulant intake over time as compared to male rats and mice (Carroll et al. 2005; Reichel et al. 2012; Melon et al. 2013; Roth and Carroll, 2004; George et al. 2021). Female rats and mice also self-administer more heroin during the first hour of a long, continuous access session (fixed-ratio 1, 6-h session; Towers et al. 2019) and more fentanyl within active trials under the intermittent access procedure (Towers et al. 2022), have longer initial periods of “binge” cocaine intake (defined as continuous drug use with no breaks from drug self-administration greater than 1 hour) and greater dysregulation in diurnal patterns of cocaine intake under 24-hr/day discrete trial procedure (Lynch and Taylor, 2004), and have greater binge-like alcohol drinking under the “drinking-in-the-dark” procedure as compared to males (defined as the amount of ethanol consumed during the first 3-hours of the dark phase; e.g., Sneddon et al. 2019). These findings indicate that females are more vulnerable than males to excessive drug use and developing a loss of control over drug use. This sex difference also appears to be robust as it has been observed in several species and for multiple drugs.

Importantly, the sex differences observed for the development of an addiction-like phenotype mirror findings of a telescoping effect in women and indicate that this phenotype develops more readily in female as compared to male animals (**Table 3**; Lynch 2018; Lynch and Taylor 2004; Perry et al. 2013; Ramôa et al. 2013; 2014). This work has focused on effects with cocaine with results from the initial study of sex differences showing that females, but not males, developed an enhanced motivation for cocaine under conditions predicted to be threshold for inducing this phenotype (**Figure 2;** 7 days of extended-access cocaine self-administration and 10 days of abstinence; Lynch and Taylor, 2004). We subsequently confirmed that this phenotype is absent in both females and males when assessed under sub-threshold self-administration and abstinence conditions (e.g., extended-access self-administration with no intervening period abstinence or

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

following short-access self-administration with or without abstinence; Lynch and Taylor, 2005), and present in both sexes when the conditions are optimized for its development by lengthening the period of extended-access self-administration (i.e. 10 days) and/or the abstinence period (i.e. 14 days; Roberts et al. 2007; Ramôa et al. 2013; Kawa et al. 2019).

We firmly established a telescoping effect with cocaine in our more recent studies by demonstrating that three key features of SUD, an enhanced motivation for the drug, compulsive drug use, and enhanced drug-craving/vulnerability to relapse, develop sooner during abstinence following extended-access self-administration in females than in males (Towers et al. 2021; Towers et al. revised submission). Specifically, an enhanced motivation for cocaine was evident in females after 7 days of abstinence, whereas, in males it is not evident until after 14 days. Females tested after 7 days of abstinence also displayed greater compulsive cocaine use than males, and while males reached the same level of resistance to punishment as females, this did not occur until after 14 days of abstinence. We also found that in females, cocaine-craving, as defined by total drug-seeking during extinction and cue-induced reinstatement testing, was expressed at high levels during both early and late abstinence, whereas, in males, drug-craving progressively increased from early to later abstinence time-points (following 2 versus 14 days) (Towers et al. revised submission). Notably, once these addiction-like features develop, sex differences are subtle and some studies show greater effects in females than males (e.g., Towers et al. 2021) while others show no differences (e.g., Ramôa et al. 2013). Estrous cycle effects still appear to be relevant though considering that numerous studies have shown that drug-craving following abstinence from extended-access self-administration is higher in females tested during estrus versus non-estrus phases (Corbett et al. 2021). Together, these findings show that an

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

addiction-like phenotype with cocaine develops at an accelerated rate in female rats compared to male rats and indicate that the parallel effect in women is biologically-based.

It is important to determine if similar sex differences occur for other drug classes. The initial findings with fentanyl suggest that both the time-course for the development of an addiction-like phenotype and the occurrence of sex difference may be different for opioids. Specifically, Townsend et al. (2021) found that males prefer low doses of fentanyl over a non-drug reinforcer (i.e., Ensure) while females required a higher dose of fentanyl to shift their preference from Ensure. In males, preference for fentanyl increased progressively following repeated cycles of extended-access self-administration and withdrawal (8 hours); whereas, in females, preference for highest dose of fentanyl decreased during acute withdrawal. While these findings were interpreted to reflect a greater sensitivity in males than females to developing a preference for fentanyl over a non-drug reward, it is notable that even in males the preference observed for fentanyl following the third 1-week cycle of extended-access self-administration and withdrawal was not significantly greater than that observed for the non-drug reward (~50%), and in females, the non-drug reward was strongly preferred (~75%). Considering that both males and females showed a strong preference for high doses of fentanyl prior to extended-access self-administration, this phenotypic difference may be indicative of a sex difference of acute fentanyl withdrawal rather than a sex difference in the development of an addiction-like phenotype. In fact, a similar sex difference was observed with cocaine. Female rats tested following extended-access cocaine self-administration, without an intervening period of abstinence, showed a marked decrease in motivation for cocaine whereas, male rats did not show a change from baseline (i.e., prior to extended-access self-administration; Lynch and Taylor, 2005). One caveat to this interpretation, however, is that in males the behavioral phenotype was validated by

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

showing that withdrawal-associated increases in heroin intake were blocked using methadone, an FDA-approved treatment for opioid use disorder (OUD). Further research comparing phenotypic changes in females versus males over a period of protracted abstinence following extended-access opioid is necessary to determine whether there are sex differences in the time-course for the development of addiction-like features with opioids.

Sex differences have also been observed for the expression of addiction-like features following short-access self-administration, particularly when behavior is examined following a prolonged period of self-administration (1-2 hr/day access for 30 or more days). For example, several studies have shown that the development of a preference for the drug (cocaine) over another competing reinforcer (food), another key characteristic of SUD in humans, occurs more readily in females than males tested over a prolonged period of short-access cocaine self-administration (~3-5 weeks; Kerstetter et al. 2012, Perry et al. 2013, Perry et al. 2015); this preference also developed in a greater percentage of females than males (~50% versus 17%, respectively; Perry et al. 2015). The development of a preference for cocaine over food was also associated with the development of two other key addiction-like features, an enhanced motivation for the drug and heightened drug-craving, indicating that females are more vulnerable than males to developing an addiction-like phenotype.

2.4 Summary and Integration of Preclinical and Clinical Findings

Together, these findings indicate that female laboratory animals display a greater vulnerability than male laboratory animals during the transition from initial drug use to the development of an addiction-like phenotype. Female animals take more psychostimulants, opioids, and alcohol and show greater escalation/binge intake under extended-access conditions than male animals.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Female animals also develop an enhanced motivation for cocaine and a preference for cocaine over other reinforcers after less drug exposure and/or shorter periods of abstinence than male animals. It is important to emphasize, however, that the preclinical evidence demonstrating a faster time-course for the development of addiction-like features in females than males is based exclusively on findings with cocaine. To our knowledge, no studies have examined sex differences in the time-course for the development of addiction-like features following protracted abstinence from extended-access self-administration with other addictive drugs. While the preclinical findings with cocaine provide strong support for its biological basis, future research studies are necessary to determine if females also show an accelerated course for the development of addiction-like features in animal models of alcohol, opioid, and other psychostimulant use disorders. These studies are especially important considering that a telescoping effect has consistently been reported in women for cocaine use disorder (CoUD), in both treatment and non-treatment populations, which is in contrast to the findings for AUD and OUD. Future research is also necessary to address molecular mechanisms underlying the telescoping which, as discussed below, are currently unknown.

3. Biological Factors

3.1 Ovarian Hormones

Most of the work on potential mechanisms for sex differences in SUD has focused on the role of ovarian hormones. In clinical research, menstrual phase is often used as a proxy for ovarian hormones; several caveats to these studies need to be mentioned. First, it is essential that cycle stage is confirmed by hormone measurements. Without this confirmation it is likely that non-ovulatory cycles and/or cycles with insufficient luteal phase will be included (Younis 2020). In

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

addition, self-reported cycle lengths are often not accurate (Small et al, 2007). Women with polycystic ovarian disease and/or metabolic syndrome need to be excluded as do women on oral contraceptives since their cycles are anovulatory.

3.1.1 Human Studies – Ovarian Hormones and Substance Use

There is a large body of literature documenting fluctuations in the subjective and physiological effects of addictive drugs and patterns and motivation for drug use across the menstrual cycle phase (see Becker and Koob, 2016; Lynch et al. 2002 for reviews). Studies with psychostimulants have focused predominantly on the subjective and physiological effects of cocaine (in individuals with a cocaine use disorder) and amphetamine (in recreational users or "healthy controls"). These results indicate that the subjective/reinforcing effects of stimulants are higher in women during the late follicular phase, when levels of estradiol are high and progesterone levels are low, versus the mid-luteal phase, when levels of estradiol are moderate and progesterone levels are high (Lukas et al. 1996; Sofuoglu et al. 1999; Justice and de Wit, 1999; Evans et al. 2002; White et al. 2002). Similar conclusions of a faciliatory effect of estradiol and inhibitory effect of progesterone have been reached from clinical studies following exogenous hormone manipulation (Justice and deWit 2000; Lile et al. 2007; DeVito et al. 2014). For example, Lile and colleagues conducted a pilot study in 10 women without a SUD to determine the effects of exogenously administered estradiol on subjective ratings of d-amphetamine. They found that estradiol modestly increased the positive subjective effects (e.g., Like Drug) and discriminative stimulus effects of a low dose of d-amphetamine (Lile et al. 2007; also see Justice and deWit 2000). Conversely, administration of exogenous progesterone has been shown to decrease the positive subjective effects of psychostimulants in both normal

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

controls and women with SUD (Peltier and Sofuoglu 2018; Evan and Foltin, 2006; Sofuoglu et al. 2002, 2004). Similar findings of enhanced positive subjective effects during the follicular versus luteal phase have been observed for nicotine in smokers (DeVito et al. 2014). While effects with opioids have focused on analgesic effects, these findings similarly show greater morphine analgesia in women during the follicular versus luteal phase (Ribeiro-Dasilva et al. 2011). These findings indicate that estradiol enhances, while progesterone reduces, the positive subjective effects of addictive drugs, particularly psychostimulants although future studies using larger samples are needed to verify the effects of estradiol. Additional studies are also needed to determine if these effects also translate to other addictive drugs, such as opioids and cannabis.

There is also a large literature on alcohol documenting menstrual cycle effects in social drinkers and individuals with an AUD, but in contrast to literature on psychostimulants, most of these studies have focused on levels of use and craving (Terner and de Wit, 2006) rather than subjective effects (but see Evans and Levin 2011). The results have been less consistent than findings with stimulants. Some studies find greater intake and/or craving premenstrually (late luteal) and during menstruation (early follicular), whereas others show greater consumption/craving during the late follicular/ovulatory phase (see Joyce et al. 2021 for review). Affective state also fluctuates across the menstrual cycle and may overlap with changes in alcohol consumption and craving. For example, negative affect, including anxiety and depressive affect, peaks in the late luteal/premenstrual phase and early follicular/menstrual phase in response to progesterone withdrawal (Herzog 1995; Moran et al. 1998; Gallo and Smith 1993; Smith et al. 1998), and positive affect, including feelings of well-being and reward-processing, peak in the late follicular/ovulatory phase when levels of estradiol have are at their apex and progesterone levels are low (Aganoff and Boyle, 1994; Collins et al. 1985). Motivation for

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

drinking similarly varies across the menstrual cycle with women reporting increases in drinking to combat negative affect during the late luteal/menstrual phase, and increases in drinking for social motives during late follicular/ovulatory phase (Joyce et al. 2018).

3.1.2 Human Studies – Ovarian Hormones and SUD

Motivation to use alcohol and other addictive drugs also likely differ between recreational users and individuals with a SUD given that once addiction has developed, the positive subjective/reinforcing effects of drugs diminish, and the negative reinforcing effects become the principal motivator for drug use (Koob 2021). This idea is also in line with findings showing that in healthy college women (without an AUD), social drinking and craving for alcohol are increased in the follicular phase (vs luteal phase) and associated with increased levels of estradiol (Warren et al. 2021; Martin et al. 1999), whereas, in women with an AUD and/or premenstrual dysphoric disorder, alcohol craving is highest during the late luteal/early follicular phases, when negative affect is highest and progesterone levels are low (Mello et al. 1990; Svikis et al. 2006; Evans and Levin, 2011; Kiesner, 2012). Higher levels of progesterone are also predictive of lower levels of alcohol craving in postmenopausal women with AUD (Weinland et al. 2021). It is also notable that findings with psychostimulants similarly show that, in contrast to positive subjective responses, craving is predicted by progesterone levels. Craving is low when progesterone levels are high (versus when low or moderate; Sinha et al. 2007; Goletiani et al. 2015; Ethier et al. 2021) and can be offset by treatment with progesterone or its metabolite, allopregnolone (Peltier and Sofuoglu et al. 2018; Fox et al. 2013). It is also consistent with findings in smokers showing that nicotine withdrawal and depressive symptoms are increased during the late luteal phase, particularly in women who have premenstrual syndrome or

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

premenstrual dysphoric disorder (Perkins et al. 2000; Mello et al. 1990; Svikis et al. 2006; Evans and Levin, 2011; Kiesner, 2012). Findings in daily cannabis users similarly show that cannabis use is higher in the late luteal phase (premenstrually) as compared to the follicular and ovulatory phases (Hanzal et la., 2019; Joyce et al. 2021) and preliminary evidence indicates that progesterone attenuates cannabis craving (Sherman et al. 2019). To our knowledge, no studies have examined the impact of ovarian hormones or menstrual cycle on craving or use of opioids highlighting an area for future research.

Together, these findings indicate that in women the role of ovarian hormones may vary in recreational users versus individuals with a SUD. In initial stages, or under conditions wherein the positive reinforcing actions of the drug are predominantly motivating drug use, estradiol enhances the subjective effects of drugs and likely enhances vulnerability to drug use. At these times, progesterone reduces the subjective effects of addictive drugs and likely reduces vulnerability to drug use. In contrast, progesterone appears to be more critical than estradiol in motivating drug use and craving for addictive drugs in individuals with a SUD and those using addictive drugs for their negative reinforcing effects. Evidence indicates that withdrawal from progesterone enhances drug craving and/or drug use to combat negative affect/craving whereas, high levels of progesterone either during the luteal phase or after exogenous administration reduces drug craving and/or use. These results further indicate that the telescoping effect in women may be driven by reward enhancing actions of estradiol as experienced during initial drug use. In turn, this increases the probability of additional recreational use and the subsequent development of a SUD. Additional research is necessary to determine the effects of ovarian hormones on the subjective effects, levels of use, and craving for opioids.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

It is important to note that the relationship between ovarian hormones and drug use/SUD is reciprocal in that ovarian hormones both impact and are impacted by drug use and SUD. For example, during cocaine withdrawal, progesterone levels are elevated across the menstrual cycle resulting in significantly lower ratios of estradiol/progesterone as compared to healthy controls (Fox et al. 2007). This occurs in response to elevated cortisol levels and may indicate sub-fertile cycles (Dobson and Smith 1998). This response is also anxiolytic at first, but may lead to the later blunting of the stress response and increased anxiety, reduced tolerance to stress, and depression, which are all stress-related behaviors associated with relapse susceptibility in women with CUD (Fiad et al. 1996; Kaplan and Manuck 2004; Kampman et al. 2004; Sinha et al. 2006). Additionally, hypogonadism is common with chronic opioid use or opioid replacement therapy and is the result of suppression of the pulsatile release of gonadotropin-releasing hormone leading to deficiencies of luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol, and progesterone (Antony et al. 2018). Chronic alcohol use also causes hypothalamo-pituitary dysfunction and is associated with menstrual irregularities, such as anovulation, luteal-phase defects, recurrent amenorrhea, and early menopause (Hugues et al. 1980). As another example, nicotine reduces the aromatization of testosterone to estradiol, and as such, female smokers have higher testosterone levels and are more likely to experience estradiol deficiency and early menopause than nonsmoker females (Jandikova et al. 2017). Similar reciprocal effects of ovarian hormones and addictive drugs have also been observed in preclinical studies, but given that hormones can be more precisely manipulated in animals (e.g., using hormone replacement in ovariectomized, OVX, animals), these studies have been critical for establishing a causal role of ovarian hormones in substance use and SUD.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

3.1.3 Animal Studies – Ovarian Hormones and Substance Use

Most of the support for a role of ovarian hormones on vulnerability to addiction has come from preclinical studies. These studies have shown that the reinforcing effects of addictive drugs vary in intact female rodents across the estrous cycle and in OVX females with and without hormone replacement. Studies in intact females have shown that following acquisition of drug self-administration, progressive-ratio responding for cocaine is markedly higher during estrus compared to other phases of the estrous cycle (Feltenstein and See, 2007; Roberts et al. 1989; Hecht et al. 1999; Lynch et al. 2008; Lacy et al. 2016). Findings in non-human primates similarly show that progressive-ratio responding for cocaine varies across the menstrual cycle with the highest levels observed during the follicular phase (versus the late luteal phase); this effect is modest and only apparent at a low dose (Mello et al. 2007). Motivation for nicotine is also higher in female rats during estrus, but this effect is modest and has been observed in some studies (e.g., Lynch 2009), but not others (Donny et al. 2000).

Studies with alcohol have focused on consumption and have shown that consumption is lower in female rats during estrus and proestrus (versus metestrus and diestrus). However, these effects are modest and are only apparent when estrous cycles are synchronized such that each female is tested in the identical portion of each phase (Roberts et al. 1998; also see Forger and Morin, 1982). In contrast, no estrous cycle effects are observed for maintenance levels of alcohol consumption in free-cycling female rats indicating that the variability in hormone levels within different phases of the estrous cycle is enough to obscure the effects of estrous phase on drug intake. In female non-human primates, alcohol intake tends to be highest during mid-to-late follicular and the late luteal phase, which is similar to findings in humans (versus menses, Mello et al. 1984). Studies with opioids have also focused on maintenance levels of intake and have

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

shown that intake is markedly lower during proestrus as compared to other phases of the estrous cycle (Lacy et al. 2016; Smith et al. 2021; Schmidt et al. 2021). This effect appears to be driven by estradiol given that it can be blocked using raloxifene, a selective estrogen receptor modulator/antagonist, and mimicked by administering supplementary estradiol treatments (Smith et al. 2021; Sharp et al. 2021).

Studies in OVX rats have consistently found a significant role for ovarian hormones in mediating the reinforcing effects of addictive drugs. For example, numerous studies have shown that OVX robustly attenuates the acquisition of cocaine self-administration (Hu et al. 2003; Jackson et al. 2006; Lynch and Carroll, 2001; Perry et al. 2013; Hu and Becker, 2008; Zhao and Becker, 2010). It also decreases nicotine self-administration (Maher et al. 2022), the acquisition of methamphetamine and cannabinoid (WIN55,212-2, CB1 receptor agonist) self-administration (Kucerova et al. 2009; Fattore et al. 2009), and alcohol consumption and preference during acquisition and maintenance (Forger and Morin, 1982; Cailhol and Mormede, 2002). Studies with cocaine and methamphetamine further show that estradiol replacement in OVX females restores acquisition rates to those observed in ovary-intact females (Kucerova et al. 2009; Hu et al. 2003; Jackson et al. 2006; Lynch and Carroll, 2001; Perry et al. 2013; Hu and Becker, 2008; Zhao and Becker, 2010). Notably, concurrent administration of progesterone with estradiol inhibits the effect of estradiol on acquisition of cocaine self-administration (Jackson et al. 2006). Progesterone has also been shown to attenuate cocaine-induced conditioned place preference (Russo et al. 2008) and to decrease impulsive choice for cocaine in ovary-intact females (Smethells et al. 2016). Similar findings for the effects of OVX and hormone replacement have been observed for the rewarding effects of cocaine, alcohol, nicotine, methamphetamine, and amphetamine as assessed under the conditioned place preference paradigm (Hilderbrand et al.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

2018; Mirbaha et al. 2009; Chen et al. 2003; Torres et al. 2009; Silverman et al. 2007; Fry and Rhodes, 2006). These findings indicate that estradiol enhances the reinforcing effects of psychostimulants and other drugs, while progesterone reduces it, similar to reports in humans.

There are also intriguing new data that suggest that in females, hormonal status at the time of initial drug exposure/conditioning impacts later vulnerability to drug use. Specifically, Johnson et al. (2019) showed that female rats that had undergone Pavlovian conditioning with cocaine (paired with a cue light) during estrus prior to cocaine self-administration were more motivated to obtain infusions of cocaine paired with the light cue as compared to males or to females that had been conditioned during diestrus. Levels of estradiol during the time of initial exposure/conditioning appears to drive this effect considering that in OVX females estradiol supplementation that occurs prior to acquisition, effectively restores drug intake to levels observed in intact females whereas, supplemental after acquisition does not impact intake (Maher et al. 2022). It is not yet known whether hormonal status during initial drug exposure would also impact vulnerability to developing addiction-like features. Future studies using animal models of SUD are necessary to determine this possibility and to determine if effects extended to other addictive drugs.

Finally, it is important to highlight a need for additional studies to examine the impact of ovarian hormones on the reinforcing effects of opioids considering that effects of OVX and estradiol on acquisition have been mixed with one study showing facilitation (Roth et al. 2002) and another finding no effect of estradiol replacement (Stewart et al. 1996). In contrast, Smith and colleagues have shown in a series of studies that ovarian hormones markedly impact maintenance levels of opioid self-administration. Specifically, they showed that heroin intake is markedly lower in females during proestrus (Lacy et al. 2016; Smith et al. 2021; Schmidt et al.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

2021) and that this the effect could be mimicked by estradiol (in OVX and in ovary-intact females) and blocked by an estrogen receptor antagonist (in ovary-intact females; Smith et al. 2021; Sharp et al. 2021). They also showed that progesterone treatment increased heroin self-administration compared to estradiol treatment in OVX females (Smith et al. 2021; but see Smith et al. 2022). These findings suggest that effects of ovarian hormones may be more robust for maintenance opioid use than initial opioid use, but additional studies are necessary to examine this possibility. Future studies are also necessary to determine the direction of effects of estradiol and progesterone on the reinforcing efficacy of opioids (e.g., using progressive-ratio schedules, the threshold procedure, or choice procedures).

3.1.4 Animal Studies – Ovarian Hormones and SUD

Ovarian hormones also appear to underlie the enhanced vulnerability in females to developing addiction-like features, and these effects are apparent during both the induction/extended-access drug self-administration phase, where high levels of drug intake lead to the subsequent development of an addiction-like phenotype, and again, with the development of an addiction-like phenotype. As with effects on maintenance levels of drug use, effects of ovarian hormones on extended-access intake have been subtle in intact females. For example, studies on extended-access alcohol self-administration in rats have failed to demonstrate an effect of estrous cycle on alcohol intake using an intermittent access paradigm (Priddy et al. 2017) or continuous access paradigm (Ford et al. 2002) although patterns of alcohol intake do differ by estrous cycle phase (e.g., greater bout frequency and size during diestrus versus proestrus; Ford et al. 2002). Similarly, there is no effect of estrous cycle phase on levels of cocaine intake under extended-access conditions (6-h a day, Corbett et al. 2021), but during estrus, females show a greater

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

disruption in temporal patterns of cocaine self-administration (e.g., intake is more erratic/less tightly regulated) as compared to during non-estrus phases (Lynch et al. 2000). Cocaine intake also does not differ across the menstrual cycle in female non-human primates with an extensive history of cocaine self-administration (Cooper et al. 2013). These findings are in contrast to those reported by Mello et al. (2007) where menstrual cycle effects were observed for cocaine self-administration in female non-human primates that were drug-naïve prior to acquisition and progressive-ratio testing and suggest that the role of ovarian hormones may decrease from initial use to the development of an addiction-like phenotype. This conclusion is further supported by findings showing that in female rats that develop a preference for cocaine over food pellets, the estrous cycle continues to modulate motivation for food pellets, but not cocaine.

Alternatively, it is possible that effects of ovarian hormones are obscured following chronic drug self-administration due to the reciprocal effects of addictive drugs and ovarian hormones, that is, the impact of chronic drug use on ovarian hormone levels. This conclusion is supported by multiple studies with cocaine showing that depletion of ovarian hormones by OVX robustly decreases extended-access cocaine self-administration whereas estradiol replacement robustly increases levels of self-administration (Larson et al. 2007; Ramoa et al. 2013; 2014; Martinex et. al., 2016). Similar findings have been observed for alcohol consumption under a 24-hr/day, two-bottle-choice, continuous-access paradigm (Ford et al. 2004; Rajasingh et al. 2007; Becker et al. 1985; Forger and Morin, 1982 but see Hilderbrand and Lasek, 2018) and nicotine intake under extended-access conditions (Flores et al. 2016). These findings also appear to extend to opioids given our recent findings showing that OVX females with estradiol self-administer markedly higher levels of fentanyl under extended- (24-hr/day) intermittent-access conditions (2, 5 min trials/hr, 10 days) than vehicle-treated OVX rats. OVX rats with estradiol replacement, but not

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

vehicle treated OVX rats, also escalated their intake of fentanyl between the first and last extended-access sessions (Towers et al. 2022). Additionally, similar to the acquisition and conditioned place placement studies, progesterone attenuates the escalation of cocaine intake under extended-access conditions (Larson et al. 2007) and decreases alcohol consumption under a 24-hr/day, two-bottle-choice, continuous-access paradigm (Ford et al. 2002). Progesterone treatment has also been shown to decrease cocaine self-administration in intact and OVX female non-human primates with or without an extensive history of cocaine self-administration (Mello et al. 2011). Thus, estradiol appears to enhance, while progesterone protects against the transition from regular to escalated/dysregulated drug use. While additional studies are needed to determine if the protective effects of progesterone on escalation/dysregulation of cocaine and alcohol self-administration extend to other addictive drugs, such as opioids, there is strong evidence that estradiol similarly enhance vulnerability during extended-access self-administration for a number of addictive drugs, including cocaine, nicotine, opioids, and alcohol.

Findings with cocaine and opioids indicate that ovarian hormones also modulate the expression of addiction-like features following abstinence from extended-access self-administration. Most of this evidence is for drug craving and shows that levels of cocaine, fentanyl, and heroin craving are highest in females tested during estrus (versus non-estrus phases; Corbett et al. 2021; Nicolas et al. 2019; Towers et al. 2022; Bakhti-Suroosh et al. 2021); estrus also prolongs the time-course for incubation of cocaine craving in females (Kerstetter et al. 2008). While surprisingly few studies have examined the role of estradiol in incubated drug craving/relapse vulnerability following extended-access self-administration, our recent findings with fentanyl indicates that it is critically involved. Specifically, we found that OVX females with versus without estradiol replacement had a greater a sensitivity to the reinstating effects of

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

fentanyl-associated cues following extended, intermittent-access fentanyl self-administration and 14-days of abstinence (Towers et al. 2022). However, both the vehicle and estradiol treated groups showed an increase in responding following exposure to the cues indicating that while estradiol modulates the expression of this phenotype, it is not necessary for its development. Similar effects of OVX have been reported for cannabinoid-craving following short-access self-administration where OVX rats showed an attenuated response to drug-cues and drug-primes (CB_1 receptor agonist; Fattore et al. 2010). Progesterone may also be involved given that exogenous treatment has been shown to reduce cocaine-craving in intact females following short-access self-administration (Feltenstein et al. 2008 Anker et al. 2007).

In contrast to effects on drug craving, estradiol appears to be necessary for development of an enhanced motivation for the drug and an enhanced preference for the drug over other reward alternatives. Most of this work has focused on cocaine and has shown that depletion of ovarian hormones either surgically (OVX) or pharmacologically (tamoxifen treatment in ovary-intact females) prevents the development of an enhanced motivation for cocaine even under conditions optimized for its development (following extended-access self-administration and 14 days of abstinence; Bhakti-Soroush et al. 2019; Ramôa et al. 2013; 2014). In contrast, this phenotype is evident in both vehicle-treated intact females and in OVX females treated with estradiol (Bhakti-Soroush et al. 2019; Ramôa et al. 2013; 2014). Similar effects of OVX and estradiol have also been observed for the development of a preference for cocaine over food (Kerstetter et al. 2012). We also recently observed similar effects of OVX and estradiol for the development of an enhanced motivation for fentanyl (Towers et al. 2022) indicating that the role of estradiol on the development of this feature of SUD may be similar for both psychostimulants and opioids. However, further research is necessary to confirm its role with other psychostimulants (e.g.,

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

methamphetamine, nicotine) and other opioids (e.g., heroin, oxycodone). Additional studies are also needed to confirm effects with fentanyl considering that the parameters for the development of an enhanced motivation for fentanyl are not yet known (i.e., when does the phenotype emerge, how much prior drug access is needed, and how long does phenotype persist).

Interestingly, pharmacological blockade of estrogen receptors with tamoxifen has been shown to similarly prevent the development of an enhanced motivation for cocaine in ovary-intact females, but, unlike the findings in the OVX model, tamoxifen did not decrease cocaine self-administration under extended-access conditions or relapse vulnerability (Bakhti-Suroosh et al. 2019). These findings indicate that differences in level of intake during the induction/ extended-access phase, which did not differ between tamoxifen- and control-treated females, is not critical for the development of motivational features of addiction (Bakhti-Suroosh et al. 2019). They also suggest other hormones, such as progesterone, may modulate the expression of certain addiction-like features, such as a loss of control over drug use and relapse vulnerability, but perhaps not critical for others, such as an enhanced motivation for the drug. For example, where estrogen receptors are antagonized, such as with chronic tamoxifen administration in ovary-intact females, there may be compensatory decreases in progesterone signaling which leads to increased extended-access drug intake and relapse vulnerability. However, it should be noted that, as a selective estrogen receptor modulator, tamoxifen can have both agonist and antagonist effects (Dutertre and Smith 2000); thus, it is possible that its antagonist effects at estrogen receptors were sufficient for preventing the development of an enhanced motivation for cocaine, but not for reducing extended-access intake or for attenuating relapse vulnerability. Future studies are needed to resolve these questions.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

In summary, estradiol appears to enhance the expression of multiple features of SUD (loss of control over use, relapse vulnerability, preference for drug over other rewards, motivation for the drug) and to be necessary for the development an enhanced motivation for the drug and an enhanced preference for the drug over other rewards. Progesterone may attenuate the expression of addiction-like features and vulnerability maybe heightened when progesterone levels are low but additional studies are studies are necessary to confirm these possibilities.

3.2 Sex Chromosomes

One biological factor that few consider when they assess sex differences is the basic inequality in sex chromosome genes. In the mammals commonly used for preclinical studies, and in humans, males have two different sex chromosomes, X and Y, whereas females have two copies of the X-chromosome. The X-chromosome is substantially larger (3x the physical size) and contains about 1,000 more coding genes than does the Y-chromosome (Balaton et al 2018). When the phenomenon of X-inactivation was discovered, we assumed it equalized this discrepancy. If, in fact, the entire second X-chromosome in each cell was inactivated in females, the sexes would still have differences in gene expression by virtue of unique genes on the male-only Y-chromosome. However, it is now clear that many (20% in humans) X-chromosome genes escape inactivation (Disteche and Berletch, 2015; Patrat et al. 2020).

To examine the actions of sex chromosome genes both independently of hormones and interactive effects, the Four Core Genotype (FCG) mouse is frequently used (DeVries et al 2002). The dam for this cross is a normal XX female but the sire carries a null mutation of the sex determining gene (Sry) on his Y-chromosome and a transgene for the Sry that has randomly incorporated into chromosome 3 (Lovell-Badge and Robertson 1990; Mahadevaiah et al. 1998;

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Itoh et al. 2015). The Y-chromosome and the Sry transgene segregate independently producing four genetic offspring from the cross: females with XX or XY chromosome, and males with XX or XY sex chromosomes. This model provides a way to disassociate the effects of hormones from the effects of sex chromosome complement. The FCG has been exploited for over 20 years for disease models, studies of neurobiology and behavior (Gatewood et al. 2006; Quinn et al. 2007; Smith-Bouvier et al. 2008; Cisternas et al. 2018; Arnold 2020).

3.2.1 Animal Studies – Sex Chromosomes and Substance Use

One study has used the FCG mouse model to determine how sex chromosomes influence vulnerability to drug use (Martini et al. 2020). This study found that females (XX and XY) acquired cocaine self-administration faster than males XY males; XXM also acquired faster than XY males and did not differ from XX or XY females. However, contrary to findings in rats, motivation for cocaine (as assessed under progressive-ratio schedule following acquisition) was highest in XY males as compared with all other groups. Together, these results suggest sex chromosomes may interact with gonadal hormones to impact initial vulnerability to drug use.

3.2.2 Animal Studies – Sex Chromosomes and SUD

Two studies have used the FCG mouse model to examine habit formation, which is believed to occur during the transition from recreational drug use to compulsive drug use and addiction. Barker and colleagues (2010) showed that chromosomal females are slower to develop habitual responding for alcohol reinforcement compared to chromosomal males, but gonadal females consumed more alcohol than gonadal males. Interestingly, the second study showed that chromosomal females are faster to form habitual responding for sucrose compared to

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

chromosomal males, regardless of gonadal phenotype (Quinn et al. 2007). These findings suggest that sex chromosomes may differentially affect the formation of habitual drug versus non-drug reinforcers use. They also indicate that gonadal hormones, but not sex chromones, drive the enhanced vulnerability in females.

3.3 Summary and Integration of Preclinical and Clinical Findings

Together, these clinical and preclinical studies support an important role for estradiol in vulnerability during early phases of SUD, such as drug use initiation and the transition from use to SUD, thereby making estradiol a potential driver of the telescoping effect in women. These studies also highlight ovarian hormones as a potential target for intervention during initial periods of drug use and prior to the development of SUD. However, the role of ovarian hormones may be different with opioids, particularly during drug use initiation, and future studies are necessary to investigate this possibility. Finally, estradiol and progesterone have broad actions on many neural and non-neural tissues including breast, ovary and uterus. Any steroid treatments would have to take cancer risk into account.

It is important to consider that nearly all women use contraception in their lifetime (Daniels et al. 2013), and hormonal contraceptives composed of either a combination of estradiol and progesterone or progesterone alone are very popular (Cooper et al. 2022; Daniels and Joyce, 2020). Little is known about the influence of hormonal contraceptives on vulnerability to SUD in women or female laboratory animals and the clinical studies report mixed results with some showing that pill users have lower positive subjective ratings of nicotine (Hinderaker et al. 2015) and nicotine craving (Dickmann et al. 2009) than non-pill takers. However, current smokers are more likely that non-smokers to use hormonal contraceptives (Lee et al. 2013) and these women

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

have increased ethanol intake, especially if contraceptive use begins at an early age (<20 years; Lund et al. 1990). These conflicting reports could be the result of the wide range of hormonal contraceptives available to patients, which include high- versus low-doses of estradiol or just progesterone. Other characteristics of smokers versus non-smokers may also influence these results. Further studies need to determine the impact of these commonly used hormonal contraceptives as physicians could tailor their birth control recommendation if substance misuse is a concern or they could be repurposed as an adjunctive therapy for at risk adolescents since they have been proven to be safe in this patient population.

A final important consideration is pregnancy which appears to protect females. During pregnancy, progesterone and estradiol levels markedly increase and coincidentally, rates of drug use, including tobacco, alcohol, cannabis, and any drug not prescribed by a doctor to the individual, also markedly decline (Volkow et al. 2019; Kendler et al. 2017: Harrison et al. 2009). While there are obvious socio-cultural based factors that may also explain these decreased rates of drug use, studies in rats also show marked decreases in drug self-administration during pregnancy indicating that pregnancy decreases biological vulnerability to drug use in females. For example, Hecht et al. (1999) showed that in rats, motivation to obtain cocaine under short access conditions progressively declined from pre-pregnant levels over the course of pregnancy. One caution to note here, however, is that dose was not adjusted for weight changes during pregnancy, and thus motivation to obtain cocaine may be reduced by relatively low cocaine dose. However, because similar findings have also been observed for nicotine self-administration under extend-access conditions (23-hours a day; LeSage et al. 2007), where dose was adjusted for changes in body weight, and oral alcohol intake under continuous access conditions (Gene Forger and Morin, 1982) the results are likely to reflect a reduction in the reinforcing effects of

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

addictive drugs as a result of pregnancy. These effects may differ for opioids, however, considering findings showing that under short-access conditions (1-hr/day), pregnant female rats self-administer similar levels of oxycodone as non-pregnant, female rats (Vassoler et al. 2018). While these findings in rats appear to contrast with epidemiological data showing that the prevalence of past month heroin use is markedly lower in pregnant than in non-pregnant women (0.05% versus 0.19 %, respectively, 15-44 years old; Vanderziel et al. 2020), data obtained during labor and delivery show that the prevalence of opioid use and OUD in pregnant women has quadrupled over the last decade and is present in approximately 3% of pregnancies in the US (Chang 2020). Thus, the rising levels of progesterone during pregnancy appears to be protective against drug use and possibly the transition to SUD, but this may be different for opioids.

4. Neurobiological Mechanisms

4.1 Mesolimbic Dopamine Signaling

Dopamine signaling in the mesolimbic pathway has been nearly the exclusive focus of studies on molecular mechanisms mediating sex differences in SUD. This pathway, which includes dopaminergic projection neurons from the VTA to the NAc, is well established based, mainly on studies conducted in males, to be a core component of the reward circuitry and critical for mediating the positive reinforcing effects of addictive drugs (for review see Pierce and Kumaresan, 2006; Koob and Volkow). Addictive drugs increase dopamine concentrations in the NAc, and antagonizing dopamine receptors, particularly dopamine D1-receptors (D1 and D5, referred to as D_1 hereafter), prevents the acquisition of drug self-administration and decreases short-access drug self-administration (see Volkow and Morales, 2015 for review).

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Not surprisingly, the mesolimbic reward pathway is also implicated in the disease state of addiction. Again, these data are based predominantly on effects in men and male laboratory animals and show that neuroadaptations caused by chronic drug use leads to mesolimbic hypofunction, which in turn promotes drug use to combat negative affect/anhedonia induced by dopamine deficits during abstinence (Koob and Volkow, 2016). For example, it is well established based on positron emission tomography (PET) imaging studies in humans that individuals with a SUD have marked decreases in dopamine D2 receptor binding (D2, D3, and D4, referred to as D_2 hereafter) in the striatum. This molecular switch was first documented by Volkow and colleagues who showed that individuals with cocaine use disorder had lower D_2 receptor availability that corresponded to increased ratings of dysphoria which persisted months after abstinence (relative to healthy individuals, Volkow et al. 1990; 1993; 1996). These individuals also showed diminished dopamine release in the striatum and reported lower ratings of positive subjective effects (reduced liking, euphoria) and higher ratings of negative subjective effects (want more, craving) following psychostimulant administration as compared to healthy individuals (Volkow et al. 1996; 1997). This phenomenon has been replicated in many subsequent studies and for multiple SUDs including methamphetamine, nicotine, heroin, and alcohol (alcohol Martinez et al. 2005; Volkow et al. 2001, 2014; van de Giessen et al. 2017; Martinez et al. 2004, 2005, 2011, 2012; Christoph Fehret al. 2008; Worhunsky et al. 2017; but see Casey et al. 2014; for review see Volkow et al. 2007). This is thought to reflect a shift from positive reinforcing effects, a primary mechanism driving drug use during initial phases of SUD, to negative reinforcement, which drives drug use once addiction has developed to alleviate withdrawal, craving, or negative affect. A similar blunting of the dopaminergic response to psychostimulant drug administration is observed in cannabis use disorder (CaUD), and while this

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

effect is also associated with increased relapse vulnerability, it is not accompanied by a downregulation of D_2 receptors (Volkow et al. 2014). A few studies have included both men and women (Martinez et al. 2012; Volkow et al. 2001), and some sex differences have been noted (as discussed below; Brown et al. 2012; Okita et al. 2016; Wiers et al. 2016; Zakiniaeiz et al. 2019). Results from preclinical studies have revealed similar changes in D_2 receptor signaling with evidence to further indicate that mesolimbic D_2 receptor signaling contributes to both vulnerability to drug use and the development of key addiction-like features, such as a loss of control/escalation of drug use (for review see Everitt et al. 2008; Trifilieff et al. 2017). There is also compelling evidence indicating the role of dopamine is minimized once SUD is established, and that other signaling pathways, particularly those involved in mediating the negative reinforcing effects due to craving, are recruited and drive the enhanced motivation for the drug (e.g., glutamatergic signaling; see Glutamate section below).

While most of the evidence for sex differences in dopaminergic signaling is focused on initial vulnerability, preliminary findings indicate that the mechanisms underlying SUD are different in males versus females and that molecular shifts that contribute to its development occur faster in females than males (as discussed below).

4.1.1 Human Studies – Dopamine and Substance Use

Clinical studies using healthy controls, report that men and women have similar D_2 receptor availability and densities in the striatum, but women have greater dopamine synthesis capacity and dopamine transporter availability in the striatum than men (for review see Woodcock et al. 2020). The net effect is that dopamine secretion and transport are more active in women than in men. Findings for evoked dopamine release in the striatum however, have been mixed, and tend

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

to suggest greater effects in healthy men than women in response to psychostimulants and alcohol (Munro et al. 2006; Urban et al. 2010; Oswald et al. 2015; Smith et al. 2019; but see Riccardi et al. 2006). In contrast, Manza and colleagues (2022) reported more striatal dopamine release in women than men (as measured by displacement of [^{11}Craclopride]) in response to both oral and intravenous administration of the psychostimulant methylphenidate. Women also reported higher ratings of "drug effects" than men (Manza et al. 2022), which is in contrast to the other studies reporting greater psychostimulant-evoked dopamine release and positive subjective effects in men than in women (Munro et al. 2006; Smith et al. 2019). Given that the positive subjective effects of addictive drugs are believed to be driven by mesolimbic dopamine signaling, this difference provides a plausible explanation for the differences between these results. Moreover, as with positive subjective ratings of addictive drugs, sex differences in evoked dopamine release are influenced by hormonal changes over the menstrual cycle. Cycle day and/or hormone data have not been included in some of the previous studies (Munro et al. 2006; Urban et al. 2010; Oswald et al. 2015) or testing was completed in women with low ovarian hormones (Munro et al. 2006; Oswald et al. 2015; Smith et al. 2019). As a specific example, in the Smith et al. (2019) study, the women included were in one of three low estradiol states; either postmenopausal, on hormonal contraceptives, or in the early follicular phase of their menstrual cycle. This is in contrast to the most recent study where hormone data were collected and at least some of the women included were tested during the mid-to-late follicular phase (Manza et al. 2022), when levels of estradiol are high and relatively unopposed by progesterone. However, even in this recent study, details are lacking regarding menstrual cycle status and estradiol levels are available for only 7 of the 11 female subjects. Future studies that measure, or manipulate, levels of estradiol and progesterone are necessary to resolve this issue.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

4.1.2 Human Studies – Dopamine and SUD

Most of the studies on sex differences in dopamine signaling and SUD have been conducted among tobacco smokers. These studies have shown, that as with findings in individuals with CoUD, AUD, and OUD, individuals with a TUD have a blunted dopamine response to psychostimulant administration (Busto et al. 2009; Wiers et al. 2017; Calakos et al. 2022; Zakiniaeiz1 et al. 2019), with particularly robust effects in women (Cosgrove et al. 2014; Zakiniaeiz et al. 2019). There is also a sex difference in the mechanism underlying this effect. In male smokers, the mechanism appears to be similar to that observed for CoUD, OUD, and AUD, decreased striatal D_2 receptor binding (Brody et al. 2004; Fehr et al. 2008; Stokes et al. 2012; Albrecht et al. 2013a; Brown et al. 2012). This is not the case in female smokers, however, since striatal D_2 receptor binding does not differ between smokers and non-smokers (Brown et al. 2012; Zakiniaeiz et al. 2019). This is intriguing considering that in male smokers this molecular shift is thought to reflect greater addiction severity and poorer treatment outcomes (Volkow et al. 1999); yet this does not occur in women who show greater addiction severity and worse treatment outcome than males. It is similarly thought to reflect enhanced vulnerability in individuals with a CoUD, AUD, or OUD, but given that these studies have been conducted predominantly in men, it is possible that this molecular shift occurs in males but not females.

Sex differences and effects of smoking status have also been between reported for D_2 receptor availability in the midbrain, which includes the VTA (Okita et al. 2016). Female smokers have higher midbrain D_2 receptor availability than both female non-smokers and male smokers; however, no differences are seen between male smokers and non-smokers (Okita et al. 2016). This difference is thought to underlie the greater suppression of mesolimbic dopamine in women versus men smokers given that D_2 receptors are predominantly inhibitory. These

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

differences also parallel sex differences in positive subjective ratings of nicotine and smoking, which have consistently been lower in women than in men with a TUD (for review see Perkins, 1999); whereas, among non-smokers, women are more sensitive than men to low doses of nicotine (MacLean et al. 2021). Taken together, these findings indicate that there are sex differences in the molecular mechanisms underlying tobacco use/smoking with the development of TUD. The different mechanisms likely lead to sex difference in motivation to use tobacco/nicotine and a greater shift in women than in men to negative reinforcement and to a diminished role of dopamine. This explanation is also consistent with data showing that smoking in women with a TUD does not produce ventral striatal activation, but does so in men with a TUD (Verplaetse et al. 2018). Nicotine replacement is also a less effective treatment strategy for TUD in women than men (Perkins et al. 2018). While future studies are necessary to determine whether similar sex differences exist for other SUDs, it is notable that sex differences in positive subjective drug effects are observed across multiple drug classes and parallel these effects with TUD and typically show greater effects in women than men among recreational drug users, particularly at low doses (Liechti et al. 2001; Mayo et al. 2019; Vandersickel et al. 2010; Fogel et al. 2017; Miller et al. 2009; Wright et al. 2021), but no difference, or a diminished response in women versus men among individuals with a SUDs (e.g., Lynch et al. 2008; McCane-Katz et al. 2008). Additionally, de Wit and colleagues (2012) showed that dopamine depletion using a dietary intervention biases women, but not men, towards habitual responding rather than goal-directed behavior, indicating that women are prone to transition from recreational drug use, which is goal-directed, to compulsive use, which is habitual.

Individuals with a CaUD also have blunted dopaminergic responses to psychostimulant administration (Volkow et al. 2014; van de Giessen et al. 2017), but unlike effects in CoUD,

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

AUD, and OUD, this response is not associated with lower striatal D_2 receptor availability (Albrecht et al. 2013b; Sevy et al. 2008; Stokes et al. 2012; Urban et al. 2012). The mechanisms underlying the blunted responses also differ between men and women. Specifically, Wiers et al. (2016) examined regional brain glucose metabolism in response to psychostimulant administration in men and women with CaUD versus healthy controls. They found decreased stimulant-induced metabolism in the midbrain and striatum as well as decreased glucose metabolism in the putamen and these correlated with addiction severity; however, all the effects were driven by changes in women. In men, no metabolic differences were observed between healthy controls and individuals with a CaUD. Women with a CaUD also had higher subjective ratings of craving in response to methylphenidate than healthy controls of either sex, whereas no difference was observed between healthy men and men with a CaUD (Wiers et al. 2016). These results indicate that the neuroadaptations underlying SUD differ between men and women.

Sex differences in the time-course for these molecular shifts in dopamine signaling/receptor populations that are concurrent with the development of SUD have not been examined. However, data from young adult men and women at risk for an AUD indicate they are possible. Specifically, Oswald and colleagues (2010) showed that in young adults at high risk for an AUD based on levels of drinking (>10-15 drinks/week, 15 drinks/week for males, and 18 drinks/week for females), men had greater and more widespread increases in striatal dopamine release than women in response to alcohol administration. Subjective ratings of "activation" in response to alcohol were also positively correlated with dopamine release in the ventral striatum in men, whereas subjective ratings of alcohol were not correlated with dopamine release in women. These findings suggest that the shift toward a diminished role of dopamine signaling, believed to

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

reflect greater addiction severity, may occur sooner in females than males. However, future studies are necessary to determine if this effect is reliable and consistent across SUDs.

4.1.3 Animal Studies – Dopamine and Substance Use

Results from preclinical studies also suggest that there are sex differences in the dopamine signaling pathway. Although there are divergent data on whether the density of D_1 receptors in the NAc differs between males and females (Festa et al. 2006; Andersen and Teicher 2000), markers of D_1-cAMP-PKA cell signaling, which is associated with greater vulnerability to drug use, are enhanced in drug naïve females compared to drug naïve males (Lynch et al. 2007). However, it is important to note that markers of vulnerability, which have been generated based predominantly on findings in males, may differ between males and females. For example, Morgan et al. (2002) showed that dominant male cynomolgus monkeys have higher D2 receptor availability and are less vulnerable to the reinforcing effects of cocaine as compared to subordinate male monkeys. While dominant female cynomolgus monkeys also had higher D2 receptor availability than subordinate female cynomolgus monkeys, dominant females were more vulnerable to the reinforcing effects of cocaine as compared to subordinate females (Nader et al. 2012) indicating that the relationship between D2 receptor availability and vulnerability to cocaine is opposite in females versus males.

Preclinical findings also demonstrate that ovarian hormones modulate dopaminergic signaling in the reward pathway in females. Neuron firing rates in the VTA reach peak levels in females during estrus (versus diestrus; Calipari et al. 2017), and drug-induced dopamine release is greater during proestrus/estrus (versus metestrus/diestrus; Becker and Cha, 1989; Calipari et al. 2017). Results from non-human primates show that striatal D_2 dopamine receptor availability

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

is lower during the follicular phase than the luteal phase (Czoty et al. 2009). OVX has also been shown to increase striatal D_2 receptors, reduces VTA firing rates, and drug-induced dopamine release in the NAc, while estradiol replacement restores each of these effects in female rats (Shams et al. 2016; Sham et al. 2018; Cummings et al. 2014; Zhang et al. 2008; Castner and Becker, 1993). Estradiol also increases tyrosine hydroxylase, the rate-limiting enzyme for dopamine synthesis and production, decreases sensitivity of D_2 auto receptors, enhances D_1 receptor activation (Festa et al. 2006), and reduces the reuptake of DA, all of which enhance mesolimbic DA signaling (Calipari et al. 2017). Estradiol-induced changes in dopamine signaling have been linked to an increased sensitivity to the rewarding effects of cocaine, assessed using conditioned place-preference (Calipari et al. 2017), and the reinforcing effects of alcohol (Vandergrift et al. 2017).

Interestingly, progesterone can both potentiate and inhibit estradiol's effects on dopamine release with enhancement observed shortly after estradiol and progesterone administration in OVX rats and inhibition observed 24-hr after administration (Glaser et al. 1983). These differences likely explain estrus-induced enhancements of dopamine release given that both estradiol and progesterone peak prior to the beginning of estrus (Becker and Ramirez, 1981; Becker and Rudick, 1999; Dluzen and Ramirez, 1984; Becker et al. 1984; see Yoest et al. 2018 for review). Thus, estradiol enhancement of mesolimbic dopamine signaling appears to increase the rewarding and reinforcing properties of addictive drugs and likely drives the enhanced sensitivity in females during initiation/acquisition of drug use. While similar effects have been observed for cocaine, amphetamine, and alcohol, further research is necessary to determine if findings extend to other drug classes, including opioids and cannabis.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

4.1.4 Animal Studies – Dopamine and SUD

While dopamine-estrogen interactions likely contribute to the enhanced sensitivity in females during initiation/acquisition of drug use (for review see Kokane and Perrotti 2020), it is not yet clear if similar mechanisms underlie vulnerability during later phases of SUD or the faster time-course to addiction in females versus males. Such effects are possible given findings from multiple studies showing that estradiol increases cocaine, alcohol, nicotine, and fentanyl intake under extended-access conditions (Larson et al. 2007; Ramoa et al. 2013; 2014; Martinex et. al., 2016; Ford et al. 2004; Flores et al. 2016; Towers et al. 2022). Findings with alcohol also show that estradiol potentiates alcohol-induced excitation of dopamine neurons in VTA and that targeted knockdown of estrogen receptors in the VTA reduces binge alcohol drinking in female, but not male mice (Vandergrift et al. 2017; Vandergrift et al. 2020). Thus, as with effects during drug use initiation, estradiol may enhance vulnerability to the development of addiction-like features by enhancing drug-induced dopamine signaling in the reward pathway.

Estradiol may also be necessary in females for the molecular switch to a diminished role of mesolimbic dopamine that accompanies the development of an addiction-like phenotype. Specifically, we showed that OVX prevents both the development of an enhanced motivation for cocaine and the corresponding molecular shift to a diminished role of NAc dopamine and that both effects can be restored by estradiol replacement (Ramôa et al. 2013; 2014). In our work, NAc D_1 receptors remained the critical mechanism motivating cocaine use in vehicle-treated OVX rats that did not develop an addiction-like phenotype (Doyle et al. 2014; Ramôa et al. 2014). Similarly, Perry et al. (2015) showed that female rats that developed a preference for cocaine over a non-drug reward (i.e. palatable food pellets) also displayed attenuated cocaine-induced dopamine release in the NAc. In addition, the rats that developed a cocaine preference,

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

the estrous cycle continued to modulate motivation for the palatable food pellets, but not cocaine (Perry et al. 2015) indicating that ovarian hormones may not be necessary for the expression of this feature of SUD. Thus, estradiol accelerates, and is necessary, for drug-induced changes in dopamine signaling that underlie the development of addiction, but it may not be necessary for the expression of the addiction-like behaviors once they have been established (although estradiol still modulates their expression as discussed in the next section for cocaine craving).

4.2 Corticomesolimbic Glutamate

Studies in animals have established that estradiol enhances mesolimbic dopaminergic signaling via interactions with metabotropic glutamate receptors (mGlu); this likely contributes to the enhanced sensitivity in females versus males to the reinforcing effects of addictive drugs (as detailed below). Glutamatergic signaling in corticomesolimbic regions, including projection neurons from the mPFC to the NAc, is also a strong candidate mechanism underlying the faster course to addiction in females. This pathway is critical for the development of multiple features of addiction including escalation of drug use, compulsive drug use, enhanced motivation for the drug, and enhanced craving/vulnerability to relapse (Koob and Volkow, 2016). Preclinical findings indicate that estradiol interacts with metabotropic glutamate receptors (mGlu) to enhance mesolimbic dopaminergic signaling, which may contribute to the enhanced sensitivity in females versus males to the reinforcing effects of addictive drugs. Glutamatergic signaling in corticomesolimbic regions, including projection neurons from the mPFC to the NAc, is also a strong candidate mechanism underlying the faster course to addiction in females. This pathway is critical for the development of multiple features of addiction including escalation of drug use, compulsive drug use, enhanced motivation for the drug, and enhanced craving/vulnerability to

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

relapse. Glutamatergic projections from the mPFC to the NAc modulate the behavioral consequences of extended-access drug self-administration (Schmidt and Pierce 2010; Kalivas and Volkow, 2011; Quintero, 2013), and several studies have shown that extended-, but not short-access, self-administration produces long-lasting adaptations in glutamate NMDA and AMPA receptors in the mPFC and NAc in humans, non-human primates, and rats (Hemby et al. 2005; Tang et al. 2004; Backes and Hemby 2003). This signaling pathway is known as the “final common pathway to relapse” since it is activated in response to relapse triggered by drug-associated cues, priming doses of the drug, and stress, and for multiple drug classes, including psychostimulants, nicotine, opioids, and alcohol (Peters et al. 2008; Kalivas and McFarland 2003; Knackstedt and Kalivas, 2009).

Corticomesolimbic glutamate pathways also underlie the progressive increase, or incubation, of drug-craving over abstinence. Glutamatergic signaling in this pathway changes dramatically during abstinence, from hypoglutamatergic during early abstinence, when levels of drug-craving are low (first 1-3 days), to hyperglutamatergic during protracted abstinence, when craving has incubated to high levels (after 7 or more days; Barry and McGinty, 2017; Ben-Shahar et al. 2009; Caffino et al. 2020; Chen et al. 2013; Funk et al. 2016; Hearing et al. 2018; Koob and Volkow, 2016; Roura-Martínez et al. 2020; Siemsen et al. 2019; Sun et al. 2014; Szumlinski et al. 2018). NMDA receptors are critically involved in both the early-withdrawal molecular cascade that triggers the incubation of craving (Barry and McGinty, 2017), as well as the enhanced cue-induced craving following protracted abstinence (Szumlinski et al. 2018; Barry and McGinty, 2017; Chen et al. 2013). These preclinical data are also consistent with pathophysiology of SUD in humans (Enoch et al. 2014; Hafenbreidel et al. 2017). AMPAR transmission is also critically involved, and this effect appears to be driven by Ca2+-permeable (CP) AMPAR, which

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

accumulate in the synapses of neurons in the NAc core over a period of protracted abstinence following extended-, but not short-access drug self-administration (Caffino et al. 2021; Conrad et al. 2008; Murray et al. 2021; Purgianto et al. 2013; Wolf and Tseng 2012). While most of the work in this area has been conducted with cocaine, the role of the mPFC in the drug craving and relapse appears to be similar for other drug classes, including opioids, alcohol, and methamphetamine (Bauer et al. 2013; Hearing, 2018, Bossert et al. 2006; Doherty et al. 2013; Kuntz et al. 2008; Kuntz-Melcavage et al. 2009; Lalumiere et al. 2008; Rogers et al, 2008; Rubio et al. 2018; Schmidt et al. 2005; See et al. 2009; Shen et al. 2011; Mishra et al. 2017). Results from both clinical and preclinical studies also similarly show an association between heightened drug-craving/relapse and activation of the mPFC to NAc pathway (Bauer et al. 2013-alcohol; Grusser et al. 2004-alcohol, Goldstein and Volkow, 2011; See, 2009; Rubio et al. 2018; LaLumiere and Kalivas, 2008; Szumlinski and Shin, 2018; Shin et. al., 2018).

One major caveat is that the evidence implicating glutamatergic signaling in SUD is based almost entirely on findings in men and males. Data obtained from women and female animals are beginning to accumulate and they concur with the results from men and male laboratory animals indicating a critical role for glutamate in SUD. However, as detailed below, there is also preliminary evidence indicating that there are sex differences in corticomesolimbic glutamate signaling that may contribute to sex differences in vulnerability to drug use and the faster course to addiction in females.

4.2.1 Human Studies – Glutamate and Substance Use

Very few clinical studies have examined sex differences in glutamatergic signaling. In healthy controls, women had higher levels of glutamate (as assessed using magnetic resonance

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

spectroscopy) than men in the striatum, which includes the NAc and dorsal striatum (Zahr et al. 2013). Sex differences were also seen among recreational drinkers in the activation of the corticomesolimbic regions, presumably due to glutamatergic signaling. Specifically, Seo et al. (2011) showed that exposure to alcohol-related cues increased activity in corticomesolimbic regions in both men and women, but women showed greater activation than men in the frontal gyrus (middle and superior; Seo et al. 2011).

4.2.2 Human Studies – Glutamate and SUD

To our knowledge, no studies have examined sex differences in glutamatergic signaling in individuals with a SUD. However, several studies have compared the effects of stress- or cue-induced craving on activity within corticomesolimbic regions in abstinent men and women with a SUD, typically CUD. These findings have been mixed, but generally show that this circuit, presumed to be glutamatergic, is activated in both men and women (Joseph et al. 2019; Grusser et al. 2004) although the regions activated, and degree of activation, varies by sex between studies. For example, Kilts et al. (2014) showed that corticomesolimbic activity increased (as measured using regional cerebral blow flow) in both men and women following exposure to cocaine-associated cues. In women, increased activation was observed in the precentral, middle frontal, and posterior cingulate gyri, whereas in men, increased activation occurred in the caudate, right postcentral gyrus, and left insula. Li et al. (2005) showed that both men and women show activation of the mPFC in response to stress-induced craving (using stress imagery), but under these conditions, activation was greater in women than men. Similarly, Potenza et al. (2012) showed that subjective reports of craving positively correlated with corticomesolimbic activation in both men and women with a CUD (Potenza et al. 2012), but in

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

women, corticomesolimbic activation occurred in response to stress, whereas in men, activation occurred in response to drug-associated cues. It is notable that in each of these studies, sex differences were apparent in brain regions activated in response to craving, yet subjective ratings of craving were similar between men and women. These findings add to a growing body of evidence indicating that, even in the absence of behavioral differences, the mechanisms underlying SUD in men and women may differ.

4.2.3 Animal Studies – Glutamate and Substance Use

Sex differences in mGlu signaling have been reported in drug naïve laboratory animals in several brain regions, and differences in the NAc are thought to underlie the enhanced vulnerability observed in females to initial drug use. Specifically, mGlu5 appears to be required for estradiol-evoked dopamine release in the NAc in females (Song et al. 2019). In OVX rats, either an mGlu5 antagonist (MPEP) or an estrogen receptor (ICI-182 780) antagonist can block estradiol's ability to enhance amphetamine-induced dopamine release in the NAc. Thus, mGlu5 likely contributes to sex differences in the reinforcing effects of psychostimulants and possibly other addictive drugs through an estradiol-dependent manner, which could translate to greater vulnerability to initial drug use.

4.2.4 Animal Studies – Glutamate and SUD

In OVX rats, mGlu5 activation is also necessary for estradiol-induced increases in extended-access cocaine self-administration (Martinez et al. 2016). In contrast to effects of estradiol-mGlu5 on dopamine release, which are likely mediated through rapid effects of membrane-associated estrogen receptors on neuronal excitability, effects of estradiol-mGlu5 on extended-

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

access intake require repeated estradiol treatments over time indicating that changes are mediated through nuclear estrogen receptors that lead to altered synaptic plasticity. This idea is also in line with findings showing that estradiol mediates dendritic spine plasticity in the NAc through activation of mGlu5 in drug naïve control females (Peterson et al. 2015). Females also have greater increases in spine density of medium spiny neurons following chronic drug exposure (Strong et al. 2017; Wissman et al. 2011), an effect also believed to be mediated via estradiol-mGlu5 interactions (for review see Eisinger et al. 2018). Differences are most apparent in the NAc core which is significant considering that dendritic spines on medium spiny neurons in this area integrate dopamine and glutamate signaling to mediate the reinforcing and motivational properties of addictive drugs. Thus, sex differences in mGlu5 signaling may contribute to sex differences during both initial exposure and the transition from use to addiction.

Notably, we showed that following the development of an addiction-like phenotype (i.e., an enhanced motivation for cocaine), the molecular mechanisms underlying drug use shifts from NAc dopamine to AMPA receptors in both males and females (Doyle et al. 2014). We further showed that estradiol is required in females for both the mechanistic shift to a diminished role of NAc dopamine and the development of an addiction-like phenotype (Ramôa et al. 2014). Considering that this mechanistic shift appears to accompany the development of an addiction-like phenotype, and considering that this phenotype develops sooner during abstinence in females than males, it is likely that estradiol is both necessary and accelerates the behavioral and molecular shifts (Ramôa et al. 2013). This idea is also supported by findings in drug naïve rats showing that females have enhanced glutamatergic input in the NAc compared to males (Forlano and Woolley 2010); as such, they may be “primed” for the recruitment of the glutamate system.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Enhanced NAc AMPA signaling also appears to underlie the development of drug craving/vulnerability to relapse in both males and females. However, in females, these mechanisms may be ovarian hormone dependent. Specifically, Bechard et al. (2018) showed that daily treatment with ceftriaxone, which offsets cocaine-induced deficits in the cystine-glutamate exchanger and the Na+ -dependent glial glutamate transporter (GLT-1), effectively decreases cue-induced reinstatement in both male and female rats. However, in female rats, ceftriaxone was only effective in reducing craving during non-estrus phases possibly because during estrus, the protective effects of ceftriaxone were countered by estradiol-induced increases in synaptic CP-AMPA receptors (as reflected by an increase in surface expression of GluA1 in the NAc). One caveat is that these effects were observed following short-access cocaine self-administration (2-hr/day) and extinction training (2–3 weeks), which may cause different molecular adaptations than those observed following abstinence from extended-access self-administration accompanied by development of an addiction-like phenotype. However, as females are more vulnerable than males to developing addiction-like features following short-access self-administration and we observed similar results using extended-access conditions, these findings support the idea AMPA signaling is enhanced during estrus and with the development of an addiction-like phenotype.

There are also sex differences in glutamatergic signaling within mesocortical regions in drug naïve controls and following the development of an addiction-like phenotype. In drug naïve controls, females have less basal glutamatergic excitatory strength in the prelimbic region of the mPFC compared to males, but higher GluN1 subunit expression (which are ubiquitous to the NMDA receptor; Wange et al. 2015). Additionally, we recently showed that there are marked sex differences in molecular adaptations associated with the incubation of cocaine-craving. This study focused on effects in the dmPFC a region known to mediate the incubation of cocaine-

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

craving in males. As with previous reports, in males, expression of brain-derived neurotrophic factor exon IV promoter, *Bdnf-IV*, a marker of epigenetic regulation, and NMDA receptor subunits, *Grin2a*, *Grin2b*, and *Grin1*, changed in response to abstinence and relapse testing; however, in females, only *Grin1* expression was impacted. The timeline for the change in *Grin1*, the gene that encodes the GluN1 subunit of the NMDA receptor, also differed between males and females. In males, as with previous studies, *Grin1* expression was increased following relapse testing during protracted abstinence (following 14 days), whereas, in females, *Grin1* expression was increased following relapse testing during intermediate abstinence (following 7 days). These effects also corresponded to differences in cocaine-craving in response to drug-associated cues which peaked during protracted abstinence in males and during intermediate abstinence in females (i.e., following 7 versus 14 days; Towers et al., revised submission) suggesting that glutamatergic signaling in the dmPFC is recruited earlier during abstinence in females compared to males. Similar sex differences have also been reported for the effects of extended-access methamphetamine self-administration on NMDA signaling in the dmPFC (Mishra et al. 2017; Pena-Bravo et al. 2019). Effects were first characterized in males only and showed that NMDA receptor currents were increased following abstinence (8-14 days) from extended-access self-administration and were associated with an increased GluN2B surface expression (Mishra et al. 2017). The effect was confirmed in females in a more recent study that included both males and females (Pena-Bravo et al. 2019); however, this study used a shorter period of extended-access self-administration, and under these “threshold” conditions, NMDA receptor currents were increased in females, but not males, providing further support for the idea that this molecular shift develops more rapidly in females. They also showed that the increase in NMDA receptor currents in females was not affected by GluN2B antagonism in the dmPFC indicating that, in

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

contrast to effects with males, this molecular shift is independent of GluN2B NMDA receptors in females (Pena-Bravo et al. 2019). These findings are similar to our observations with cocaine showing that *Grin2b*, the gene that encodes GluN2B subunit of the NMDA receptor, was changed in males, but not females, in response to abstinence and relapse testing. These findings are intriguing and suggest that some of the molecular changes associated with the development of an addiction-like phenotype are accelerated in females versus males (*Grin1*/GluN1), while others are qualitatively different between females and males (*Grin2b*/GluN2B).

There is also evidence indicating that sex differences in the molecular adaptations induced by substance use and SUD impact the efficacy of treatments for SUD. For example, the sex differences we recently observed for relapse-associated changes in NMDA receptor gene expression in the dmPFC likely explain findings of sex difference in the efficacy of exercise as an anti-relapse intervention. Specifically, in males, dmPFC expression levels of *Grin2a* and *Grin2b*, the genes encoding the GluN2a and GluN2b subunits of NMDA receptors, were decreased during early abstinence (day 2) after extended-access cocaine self-administration. In contrast, NMDA receptor-related mRNA levels (*Grin2a and Grin2b*) were not impacted by extended-access cocaine self-administration (versus saline) or abstinence in females. We have also shown that when exercise is available during early abstinence (days 1-7) it provides long-lasting protection against relapse during protracted abstinence (on abstinence day 15), but only in males (Beiter et al. 2016). In males, the efficacy of exercise appears to be mediated by upregulating NMDA signaling in the dmPFC during early withdrawal thereby preventing a cascade of molecular events that underlie the incubation drug-craving (Abel et al. 2019). In contrast, exercise restricted to early abstinence is not effective at reducing craving during protracted abstinence in females possibly because females do not have cocaine-induced deficits

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

in dmPFC NMDA receptor signaling during early withdrawal and thus, there is not a deficit for exercise to offset. These findings highlight a need for further research on sex differences in both the neuroadaptations underlying addiction and the efficacy of potential interventions for addiction. This information is necessary to guide the development of prevention and treatment efforts for SUD in women and will also help shed light on the mechanisms underlying the telescoping effect.

4.3 Summary and Integration of Preclinical and Clinical Findings

A telescoping effect in females is supported by clinical and preclinical neurobiological evidence which indicates that in females, interactions of estradiol with dopamine and glutamate lead to an enhanced sensitivity in females to the reinforcing effects of addictive drugs and the faster course to addiction in females versus males (**Figure 1**). Enhanced reinforcing effects is evident in both women (among healthy controls) and female animals. Estradiol enhances mesolimbic dopamine signaling on its own and through interactions with mGlu5 which lead to greater dopamine release in response to addictive drugs in females versus males. This enhanced signaling may lead to a faster shift toward a diminished role for mesolimbic dopamine. This idea is supported by findings in humans showing a blunted dopaminergic response in women versus men in heavy drinkers and smokers and results showing that in women, but not men, dopamine depletion biases women toward habitual responding. Preclinical studies similarly show that in females, a shift toward a diminished role of dopamine accompanies the development of an addiction-like phenotype and requires estradiol. An addiction-like phenotype is also accompanied by a shift toward enhanced corticomesolimbic glutamatergic signaling in both males and females. AMPA signaling in the NAc is similarly enhanced in male and female animals, but one key difference is

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

that this shift likely occurs sooner in females than males and underlies the faster course to addiction in females. This idea is supported by findings in both humans and animals indicating that women (healthy controls and recreational drinkers) and female rats (drug naïve) have enhanced glutamatergic input to the striatum and are thus “primed” for the recruitment of the glutamate system.

Finally, it is important to note that sex differences in vulnerability to drug use and addiction likely involved many more brain regions (e.g., amygdala, hippocampus) and neurotransmitter signaling pathways (opioids, norepinephrine, serotonin, GABA, and endocannabinoids). To take an illustrative example, clinical and preclinical studies have shown acute stress potentiates dopamine function in the striatum, similar to acute drug use (Bloomfield et al. 2019; Imperato et al. 1989; Wand and et al. 2007). This effect appears to be mediated by glucocorticoid in the mesolimbic dopamine reward pathway since adrenalectomy, which depletes glucocorticoid hormone levels, decreases dopamine release in the NAc following stress and glucocorticoid replacement prevents attenuation of this dopamine response (Piazza and Le Moal, 1996; Barrot et al. 2000). Glucocorticoids have also been shown to potentiate the reinforcing properties of addictive drugs (Piazza et al. 1993; see review Berry et al. 2016; Piazza and Le Moal, 1997) and this effect is likely magnified in females considering psychostimulants, such as cocaine and methamphetamine, produced an even greater increase in brain glucocorticoid levels in females than in males (Kuhn and Francis, 1997; Zuloaga et al. 2014). Therefore, acute stress may prime the brain reward circuit for subsequent action of addictive drugs or act synergistically with addictive drugs to accelerate sensitization of the reward pathway.

Additionally, in contrast to acute stress, chronic stress and/or exposure to glucocorticoids has been shown to lead to anhedonia and blunting of striatal dopamine function and receptor

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

availability (Bloomfield et al. 2019; Mangiavacchi et al. 2001; Pacak et al. 2002; Meaney et al. 2002; Brake et al. 2004; Chrapusta et al. 1997; Gresch et al. 1994), similar to the neurobiological changes induced by chronic substance use (as discussed in the dopamine section). Women may be biologically more vulnerable to this stress-induced neuroadaptation considering Oswald and colleagues (2014) showed that childhood trauma is negatively associated with D_2 receptor availability in striatum of women, whereas a positive relationship was observed for men. Additionally, women often initiate drug use as a form of self-medication to reduce stress or alleviate anxiety; whereas, men are more likely to initiate drug use for their rewarding effects in social settings (see reviews, Sinha, 2001; Sinha, 2008). Thus, the stress driving initial substance use likely disrupted the reward pathway prior to drug use and enhances vulnerability to transition to SUD. All of these effects could also contribute to the faster progression to addiction observed in females.

5. Conclusions and Future Directions

The data reviewed from human, animal, and neurobiological studies supports a telescoping effect in females. The evidence is particularly strong for CoUD considering that it has been consistently observed in both treatment and non-treatment populations (McCance, Griffin, White, Haas, Sofuoglu, O'Brien; but see Lewis); preclinical studies with cocaine also similarly indicate an accelerated course to addiction in females (Kerstetter et al. 2012; Perry et al. 2013, 2015; Kawa and Robinson, 2019; Lynch and Taylor, 2004; Towers et al. 2021). The neurobiological data, which has focused almost exclusively on cocaine and other psychostimulants, also supports its biological basis with findings from both human and animal studies indicating that in females, estradiol "primes" both the dopamine reward pathway and the

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

corticomesolimbic glutamatergic pathway thereby enhancing risk of addiction. The evidence for a telescoping effect with cannabis is also strong considering that it is observed in both treatment and non-treatment seeking populations although its biological basis has not yet been established in preclinical studies. Preclinical findings with cannabinoids do suggest that females have an enhanced sensitivity to their reinforcing effects although it is not yet clear if these differences would translate to a faster course to addiction. Future research is also necessary to determine sex differences in the neurobiological effects of cannabis/cannabinoids since these effects are virtually unexplored in women and female animals.

A telescoping effect is also evident with other addictive drugs including alcohol, opioids, methamphetamine, and tobacco, but in these cases, effects may be restricted treatment populations (e.g., vulnerable individuals that develop a severe SUD). This appears to contrast with effects in preclinical studies with these compounds which indicate an enhanced vulnerability in females for both use and the development of addiction-like features (excessive drug use and a loss of control over drug use under extended-access drug self-administration conditions). Neurobiological differences between males and females would also be presumed to impact psychostimulants and many of these drugs similarly; however, much less is known on sex differences in the neurobiological effects of alcohol, opioids, nicotine, and methamphetamine. Additionally, to date, no studies have examined sex differences in the time-course for the development of addiction-like phenotype with alcohol, opioids, methamphetamine, or tobacco. Such studies are necessary since they will determine whether females are biologically-biased to have an accelerated course to addiction with these drugs. Future epidemiological studies are also needed to determine gender differences in trajectories to addiction using models that control for

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

known differences between men and women with regard to probabilities of drug use, SUD, and seeking treatment for SUD.

Future studies are necessary to identify intervention strategies for women to prevent the development of a SUD. In addition to the obvious need for additional research on hormone-based strategies, medications that target mGlu5 may have therapeutic potential in women considering that mGlu5 likely enhances both initial vulnerability to drug use and the development of addiction in females. mGlu5 is being considered as a therapeutic target for several disorders (addiction, bulimia nervosa, schizophrenia) and compounds are available for use in both humans and animals (e.g., Mihov et al. 2020). mGlu5 was recently shown to be dysregulated in the striatum of individuals, mainly men (13 of 16), with SUD; normalization of these receptors over a period of protracted abstinence was also associated with decreased craving (Ceccarini et al. 2020). Preclinical studies have also noted sex differences in the effects of Glu5 manipulations on drug-related behaviors, including findings showing that Glu5 antagonism is more effective at decreasing binge alcohol drinking in females than males (Cozzoli et al. 2014). A better understanding of sex differences in the time-course for the disease progression and the underlying mechanisms is critical for the development of sex-specific personalized medicine approaches for the prevention and treatment of SUDs.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Eleanor Blair Towers, Ivy L. Williams, Emaan I. Qillawala, Emilie F. Rissman, Wendy J. Lynch

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

References

Abel JM, Bakhti-Suroosh A, Grant PA, Lynch WJ (2019) Mechanisms underlying the efficacy of exercise as an intervention for cocaine relapse: a focus on mGlu5 in the dorsal medial prefrontal cortex. Psychopharmacology (Berl) 236:2155-2171.

Adelson M, Linzy S, and Peles E (2018) Characteristics and outcome of male and female methadone maintenance patients: MMT in Tel Aviv and Las Vegas. Substance Use & Misuse 53:230-238.

Agabio R, Campesi I, Pisanu C, Gessa GL, Franconi F (2016) Sex differences in substance use disorders: focus on side effects. Addict Biol 21:1030-1042.

Aganoff JA and Boyle GJ (1994) Aerobic exercise, mood states and menstrual cycle symptoms. Journal of Psychosomatic Research 38:183-192.

Ahmed S and Koob G (1998) Transition from Moderate to Excessive Drug Intake: Change in Hedonic Set Point. Science 282:298—300

Allain F, Minogianis EA, Roberts D, and Samaha AN (2015) How fast and how often: The pharmacokinetics of drug use are decisive in addiction. Neuroscience & Biobehavioral Reviews 56:166—179

Alvanzo AAH, Storr CL, Flair LL, Green KM, Wagner FA, and Crum RM (2011) Race/ethnicity and sex differences in progression from drinking initiation to the development of alcohol dependence. Drug Alcohol Depend 118:375-382.

American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders, 5th ed. doi:10.1176/appi.books.9780890425596.

Anderson SL and Teicher MH (2000) Sex differences in dopamine receptors and their relevance to ADHD. Neuroscience and Biobehavioral Reviews 24:137-141.

Anglin MD, Hser YI, and McGlothlin WH (1987) Sex differences in addict careers. 2. becoming addicted. American Journal of Drug and Alcohol Abuse 13:59-71.

Anker JJ, Larson EB, Gliddon LA, Carroll ME (2007) Effects of progesterone on the reinstatement of cocaine-seeking behavior in female rats. Experimental and Clinical Psychopharmacology 15:472-480.

Antony T, Alzaharani SY, El-Ghaiesh (2020) Opioid-induced hypogonadism: pathophysiology, clinical and therapeutics review. Clin Exp Pharmacol Physiol 47:741-750.

Arfken CL, Klein C, di Menza S, Schuster CR (2001) Gender differences in problem severity at assessment and treatment retention. Journal of Substance Abuse Treatment 20:53-57.

Arnold A (2020) Four Core Genotypes and XY* mouse models: Update on impact on SABV research. Neuroscience & Biobehavioral Reviews 119:1-8

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Ashley MJ, Olin JS, and Harding le Riche W (1977) Morbidity in alcoholics: evidence for accelerated development of physical disease in women. Archives of Internal Medicine 137:883-887.

Bach A, Clausen B, Kristensen L, Andersen M, Ellman D, Hansen P, Hasseldam H, Heitz M, Ozcelik D, Tuck E, et al. (2019) Selectivity, efficacy and toxicity studies of UCCB01-144, a dimeric neuroprotective PSD-95 inhibitor. Neuropharmacology 150:100—111

Back SE, Lawson KM, Singleton LM, and Brady KT (2011) Characteristics and correlates of men and women with prescription opioid dependence. Addictive Behaviors 36:829-834.

Backes E and Hemby S (2003) Discrete Cell Gene Profiling of Ventral Tegmental Dopamine Neurons after Acute and Chronic Cocaine Self-Administration. Journal of Pharmacology and Experimental Therapeutics 307:450-459

Bakhti-Suroosh A, Nesil T, and Lynch WJ (2019) Tamoxifen blocks the development of motivational features of an addiction-like phenotype in female rats. Frontiers in Behavioural Neuroscience 13:253.

Bakhti-Suroosh A, Towers EB, and Lynch WJ (2021) A bupernorphine-validated rat model of opioid use disorder optimized to study sex differences in vulnerability to relapse. Psychopharmacology 238:1029-1046.

Balaton B, Dixon-McDougall T, Peeters S, and Brown C (2018) The eXceptional nature of the X chromosome. Human Molecular Genetics 27:R242–R249

Balster RL and Woolverton WL (1982) Intravenous buspirone self-administration in rhesus monkeys. The Journal of Clinical Psychiatry 43:34-37.

Bari A and Pierce R (2005) D1-like and D2 dopamine receptor antagonists administered into the shell subregion of the rat nucleus accumbens decrease cocaine, but not food, reinforcement. Neuroscience 135:959-968

Barker J, Torregrossa M, Arnold A, and Taylor J (Dissociation of Genetic and Hormonal Influences on Sex Differences in Alcoholism-Related Behaviors. Journal of Neuroscience 30:9140-9144

Barrot, M., Marinelli, M., Abrous, D. N., Rougé-Pont, F., Le Moal, M., & Piazza, P. V. (2000). The dopaminergic hyper-responsiveness of the shell of the nucleus accumbens is hormone-dependent. European Journal of Neuroscience, 12(3), 973-979.

Barry S and McGinty J (2017) Role of Src Family Kinases in BDNF-Mediated Suppression of Cocaine-Seeking and Prevention of Cocaine-Induced ERK, GluN2A, and GluN2B Dephosphorylation in the Prelimbic Cortex. Neuropsychopharmacology 42:1972–1980

Barry SM and McGinty JF (2017) Role of Src family kinases in BDNF-mediated suppression of cocaine-seeking and prevention of cocaine-induced ERK, GluN2A, and GluN2B dephosphorylation in the prelimbic cortex. Neuropsychopharmacology 42:1972-1980.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Bauer J, Pederson A, Scherbaum N, Bening J, Patschke J, Kugel H, Heindel W, Arolt V, Ohrmann P (2013) Craving in alcohol-dependent patients after detoxification is related to glutamatergic dysfunction in the nucleus accumbens and the anterior cingulate cortex. Neuropsychopharmacology 38:1401-1408.

Bechard AR, Hamor PU, Schwendt M, Knackstedt LA (2018) The effects of ceftriaxone on cue-primed reinstatement of cocaine-seeking in male and female rats: estrous cycle effects on behavior and protein expression in the nucleus accumbens. Psychopharmacology (Berl) 235:837-848.

Becker HC, Anton RF, De Trana C, and Randall CL (1985) Sensitivity to ethanol in female mice: effects of ovariectomy and strain. Life Sciences 37:1293-1300.

Becker J and Hu M (2008) Sex differences in drug abuse. Frontiers in Neuroendocrinology 29:36—47

Becker J and Koob G (2016) Sex Differences in Animal Models: Focus on Addiction. Pharmacological Reviews 68:242—263

Becker JB (1990) Direct effect of 17β-estradiol on striatum: sex differences in dopamine release. Synapse 5:157-164.

Becker JB and Cha JH (1989) Estrous cycle-dependent variation in amphetamine-induced behaviors and striatal dopamine release assessed with microdialysis. Behav Brain Res 35:117-125.

Becker JB and Ramirez VD (1981) Sex differences in the amphetamine stimulated release of catecholamines from rat striatal tissue in vitro. Brain Res 204:361-372.

Becker JB and Rudick CN (1999) Rapid effects of estrogen or progesterone on the amphetamine-induced increase in striatal dopamine are enhanced by estrogen priming: a microdialysis study. Pharmacology, Biochemistry and Behavior 64:53-57.

Bedi G, Preston K, Epstein D, Heishman S, Marrone G, Shaman Y, and Wit H (2011) Incubation of Cue-Induced Cigarette Craving During Abstinence in Human Smokers. Biological Psychiatry 69:708—711

Beiter, R. M., Peterson, A. B., Abel, J., & Lynch, W. J. (2016). Exercise during early, but not late abstinence, attenuates subsequent relapse vulnerability in a rat model. Translational Psychiatry, 6(4), e792-e792.

Belin D and Deroche-Gamonet V (2012) Responses to Novelty and Vulnerability to Cocaine Addiction: Contribution of a Multi-Symptomatic Animal Model. Cold Spring Harb Perspect Med 2:a011940.

Ben-Shahar O, Obara I, Ary A, Ma M, Mangiardi M, Medina R, and Szumlinski K (2009) Extended daily access to cocaine results in distinct alterations in Homer 1b/c and NMDA receptor subunit expression within the medial prefrontal cortex. Synapse 63:598–609

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Berry, A., Raggi, C., Borgi, M., & Cerulli, F. (2016). Sex-driven vulnerability in stress and drug abuse. Annali dell'Istituto Superiore di Sanità, 52(2), 167-175

Bloomfield MAP, McCutcheon RA, Kempton M, Freeman TP, and Howes O (2019) The effects of psychosocial stress on dopaminergic function and the acute stress response. eLife 8:e46797.

Bossert JM, Gray SM, Lu L, Shaham Y (2005) Activation of group II metabotropic glutamate receptors in the nucleus accumbens shell attenuates context-induced relapse to heroin seeking. Neuropsychopharmacology 31:2197-2209.

Brake WG, Zhang TY, Diorio J, Meaney MJ, and Gratton A (2004) Influence of early postnatal rearing conditions on mesocorticolimbic dopamine and behavioural responses to psychostimulants and stressors in adult rats. European Journal of Neuroscience 19:1863-1874.

Brecht ML, O'Brien A, von Mayrhauser C, Anglin MD (2004) Methamphetamine use behaviors and gender differences. Addict Behav 29:89-106

Brown AK, Mandelkern MA, Farahi J, Robertson C, Ghahremani DG, Sumerel B, Moallem N, London ED (2012) Sex differences in striatal dopamine D2/D3 receptor availability in smokers and non-smokers. Neuropsychopharmacology 15:989-994.

Busto UE, Redden L, Mayberg H, Kapur S, Houle S, Zawertailo LA (2009) Dopaminergic activity in depressed smokers: a positron emission tomography study. Synapse 63:681-689.

Caffino L, Moro F, Mottarlini F, Targa G, Di Clemente A, Toia M, Orru A, Giannotti G, Fumagalli F, Cervo L (2021) Repeated exposure to cocaine during adolescence enhances the rewarding threshold for cocaine-conditioned place preference in adulthood. Addict Biol doi:10.1111/adb.13012.

Caffino L, Verheij M, Roversi K, Targa G, Mottarlini F, Popik P, Nikiforuk A, Golebiowska J, Fumagalli F, and Homberg J (2020) Hypersensitivity to amphetamine's psychomotor and reinforcing effects in serotonin transporter knockout rats: Glutamate in the nucleus accumbens. BJP 177:4532–4547

Cailhol S and Mormede P (2002) Conditioned taste aversion and alcohol drinking: strain and gender differences. J Stud Alcohol 63:91-99.

Calakos KC, Hillmer AT, Angarita GA, Baldassarri SR, Najafzadeh S, Emery PR, Matuskey D, Huang Y, Cosgrove KP (2022) Recently abstinent smokers exhibit mood-associated dopamine dysfunction in the ventral striatum compared to nonsmokers: a [11C]-(+)-PHNO PET Study. Nicotine & Tobacco Research 24:745-752.

Calipari ES, Juarez B, Morel C, Walker DM, Cahill ME, Ribeiro E, Roman-Ortiz C, Ramakrishnan C, Deisseroth K, Han MH, Nestler EJ (2017) Dopaminergic dynamics underlying sex-specific cocaine reward. Nature Communications 8:13877.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Carroll M, Batulis D, Landry K, and Morgan A (2005) Sex differences in the escalation of oral phencyclidine (PCP) self-administration under FR and PR schedules in rhesus monkeys. Psychopharmacology 180:414—426

Carroll M, Lynch W, Roth M, Morgan A, and Cosgrove K (2004) Sex and estrogen influence drug abuse. Trends in Pharmacological Sciences 25:273—279

Carroll M, Morgan A, Lynch W, Campbell U, and Dess N (2002) Intravenous cocaine and heroin self-administration in rats selectively bred for differential saccharin intake: phenotype and sex differences. Psychopharmacology 161:304—313

Casey K, Benkelfat C, Cherkasova M, Baker G, Dagher A, and Leyton M (2014) Reduced Dopamine Response to Amphetamine in Subjects at Ultra-High Risk for Addiction. Biological Psychiatry 76:23-30

Castner SA and Becker JB (1993) Sex differences in striatal dopamine: in vivo microdialysis and behavioral studies. Brain Research 610:127-134.

Ceccarini J, Leurquin-Sterk G, Crunelle CL, de Laat B, Bormans G, Peuskens H, Van Laere K (2019) Recovery of Decreased Metabotropic Glutamate Receptor 5 Availability in Abstinent Alcohol-Dependent Patients. J Nucl Med. 2020 Feb;61(2):256-262

Center for Behavioral Health Statistics and Quality (2015) Treatment episode data set (TEDS): 2004-2014. State admissions to substance abuse treatment services. SAMHSA, Maryland.

Chang G (2020) Maternal substance use: consequences, identification, and interventions. Alcohol Research 40:06.

Chen HH, Yang YK, Yeh TL, Cherng CFG, Hsu HC, Hsiao SY, and Yu L (2003) Methamphetamine-induced conditioned place preference is facilitated by estradiol pretreatment in female mice. Chin J Physiol 46:169-174.

Chen YW, Barson J, Chen A, Hoebel B, and Leibowitz S (2013) Glutamatergic Input to the Lateral Hypothalamus Stimulates Ethanol Intake: Role of Orexin and Melanin-Concentrating Hormone. Alcoholism 37:123–131

Chrapusta SJ, Wyatt RJ, and Masserano JM (1997) Effects of single and repeated footshock on dopamine release and metabolism in the brains of Fischer rats. Journal of Neurochemistry 68:2024-2031.

Cisternas C, Garcia-Segura L, Cambiass M (2017) Hormonal and genetic factors interact to control aromatase expression in the developing brain. Journal of Neuroendocrinology 30

Collins A, Eneroth P, Landgren BM (1985) Psychoneuroendocrine stress responses and mood as related to the menstrual cycle. Psychosomatic Medicine 47:512-527.

Committee on Understanding the Biology of Sex and Gender Differences; Wizemann TM, Pardue ML, editors. Exploring the Biological Contributions to Human Health: Does Sex Matter?

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Washington (DC): National Academies Press (US); 2001. COMMITTEE ON UNDERSTANDING THE BIOLOGY OF SEX AND GENDER DIFFERENCES. Available from: https://www.ncbi.nlm.nih.gov/books/NBK222293/

Conrad KL, Tseng KY, Uejima JL, Reimers, Heng LJ, Shaham Y, Marinelli M, Wolf ME (2008) Formation of accumbens GluR2-lacking AMPA receptors mediates incubation of cocaine craving. Nature 454:118-121.

Cooper DB, Patel P, Mahdy H (2022) Oral Contraceptive Pills. StatPearls, Treasure Island, Florida.

Cooper ZD, Foltin RW, and Evans SM (2013) Effects of menstrual cycle phase on cocaine self-administration in rhesus macaques. Horm Behav 63:105-113.

Corbett CM, Dunn E, and Loweth JA (2021) Effects of sex and estrous cycle on the time course of incubation of cue-induced craving following extended-access cocaine self-administration. eNeuro 8:ENEURO.0054-21.2021.

Cosgrove KP, Wang S, Kim SJ, McGovern E, Nabulsi N, Gao H, Labaree D, Tagare HD, Sullivan JM, Morris ED (2014) Sex differences in the brain's dopamine signature of cigarette smoking. Journal of Neuroscience 34:16851-16855.

Cotto JH, Davis E, Dowling GJ, Elcano JC, Staton AB, Weiss SRB (2010) Gender effects of drug use, abuse, and dependence: a special analysis of results from the national survey on drug use and health. Gender Medicine 7:402-413.

Cozzoli, D. K., Strong-Kaufman, M. N., Tanchuck, M. A., Hashimoto, J. G., Wiren, K. M., and Finn, D. A. (2014). The Effect of mGluR5 antagonism during binge drinking on subsequent ethanol intake in C57BL/6J Mice: sex- and age-induced differences. Alcohol. Clin. Exp. Res. 38, 730–738.

Cummings JA, Jagannathan L, Jackson LR, Becker JB (2014) Sex differences in the effects of estradiol in the nucleus accumbens and striatum on the response to cocaine: neurochemistry and behavior. Drug Alcohol Depend 135:22-28.

Czoty PW, Riddick NV, Gage HD, Sandridge M, Nader SH, Garg S, Bounds M, Garg PK, Nader MA (2009) Effect of menstrual cycle phase on dopamine D2 receptor availability in female cynomolgus monkeys. Neuropsychopharmacology 34:548-554.

Daniels K and Abma JC (2020) Current contraceptive status among women aged 15-49: United States, 2017-2019. NCHS Data Brief 1-8. PMID: 33151146.

Daniels K and Mosher WD (2013) Contraceptive methods women have ever used: United States, 1982-2010. Natl Health Stat Report 62:1-15.

de la Fuente L, Molist G, Espelt A, Barrio G, Guitart A, Bravo MJ, Brugal MT, and the Spanish Working Group for the Study of Mortality among Drug Users (2014) Mortality risk factors and

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

excess mortality in a cohort of cocaine users admitted to drug treatment in Spain. Journal of Substance Abuse Treatment 46:219-226.

Des Jarlais DC, Feelemyer JP, Modi SN, Arasteh K, and Hagan H (2012) Are females who inject drugs at higher risk for HIV infection than males who inject drugs: an international systematic review of high seroprevalence areas. Drug Alcohol Depend 124:95-107.

DeVito EE, Babuscio TA, Nich C, Ball SA, and Carroll KM (2014) Gender differences in clinical outcomes for cocaine dependence: randomized clinical trials of behavioral therapy and disulfiram. Drug and Alcohol Dependence 145:156-167.

DeVries G, Rissman E, Simerly R, Yang LY, Scordalakes E, Auger C, Swain A, Lovell-Badge R, Burgoyne P, and Arnold A, (2002) A Model System for Study of Sex Chromosome Effects on Sexually Dimorphic Neural and Behavioral Traits. Journal of Neuroscience 22:9005-9014

Dickmann PJ, Mooney ME, Allen SS, Hanson K, and Hatsukami DK (2009) Nicotine withdrawal and craving in adolescents: effects of sex and hormonal contraceptive use. Addict Behav 34:620-623.

Diehl A, Croissant B, Batra A, Mundle G, Nakovics H, and Mann K (2007) Alcoholism in women: is it different in onset and outcome compared to men? European Archives of Psychiatry and Clinical Neuroscience 257:344-351.

DiFranza J, Savageau J, Rigotti N, Fletcher K, Ockene J, McNeill A, Coleman M, Wood C (2002) Development of symptoms of tobacco dependence in youths: 30 month follow up data from the DANDY study. Tob Control 11:228-235.

DiFranza JR, Savageau JA, Fletcher K (2007) Symptoms of tobacco dependence after brief intermittent use. Arch Pediatr Adolesc Med 161:704-710.

Disteche and Berletch (2015) X-chromosome inactivation and escape. Journal of Genetics 94:591–599

Dluzen DE and Ramirez VD (1984) Bimodal effect of progesterone on in vitro dopamine function of the rat corpus striatum. Neuroendocrinology 39:149-155.

Dobson, H., & Smith, R. F. (1998). Stress and subfertility. Reproduction in domestic animals, 33(3-4), 107-111.

Doherty JM, Cooke BM, Frantz KJ (2013) A role for the prefrontal cortex in heroin-seeking after forced abstinence by adult male rats but not adolescents. Neuropsychopharmacology 38:446 – 454.

Donny EC, Caggiula AR, Rowell PP, Gharib MA, Maldovan V, Booth S, Mielke MM, Hoffman A, and McCallum S (2000) Nicotine self-administration in rats: estrous cycle effects, sex differences and nicotinic receptor binding. Psychopharmacology 151:392-405.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Doyle SE, Ramoa C, Garber G, Newman J, Toor Z, Lynch WJ (2014) A shift in the role of glutamatergic signaling in the nucleus accumbens core with the development of an addicted phenotype. Biological Psychiatry 76:810-815.

Dutertre M, Smith CL (2000) Molecular mechanisms of selective estrogen receptor modulator (SERM) action. Journal of Pharmacology and Experimental Therapeutics, 295(2), 431-437.

Ehlers CL, Gizer IR, Vieten C, Gilder DA, Stouffer GM, Lau P, and Wilhelmsen KC (2010) Cannabis dependence in the San Francisco Family Study: age of onset of use, DSM-IV symptoms, withdrawal, and heritability. Addict Behav 35:102-110.

Eisinger KRT, Gross KS, Head BP, Mermelstein PG (2018) Interactions between estrogen receptors and metabotropic glutamate receptors and their impact on drug addiction in females. Horm Behav 104:130-137.

Enoch MA, Rosser AA, Zhou Z, Mash DC, Yuan Q, Goldman D (2014) Expression of glutamatergic genes in healthy humans across 16 brain regions; altered expression in the hippocampus after chronic exposure to alcohol or cocaine. Genes Brain Behav 13:758-768.

Ethier AR, McKinney TL, Tottenham LS, and Gordon JL (2021) The effect of reproductive hormones on women's daily smoking across the menstrual cycle. Biology of Sex Differences 12:41.

Evans SM and Foltin RW (2006) Exogenous progesterone attenuates the subjective effects of smoked cocaine in women, but not in men. Neuropsychopharmacology 31:659-674.

Evans SM and Levin FR (2011) Response to alcohol in women: role of the menstrual cycle and a family history of alcoholism. Drug and Alcohol Dependence 114:18-30.

Evans SM, Haney M, and Foltin RW (2002) The effects of smoked cocaine during the follicular and luteal phases of the menstrual cycle in women. Psychopharmacology 159:397-406.

Everitt, B. J., Belin, D., Economidou, D., Pelloux, Y., Dalley, J. W., & Robbins, T. W. (2008). Neural mechanisms underlying the vulnerability to develop compulsive drug-seeking habits and addiction. Philosophical Transactions of the Royal Society B: Biological Sciences, 363(1507), 3125-3135.

Fattore L, Fadda P, Fratta W (2009) Sex differences in the self-administration of cannabinoids and other drugs of abuse. Psychoneuroendocrinology doi: 10.1016/j.psyneuen.2009.08.008.

Fattore L, Spano MS, Altea S, Fadda P, and Fratta W (2010) Drug- and cue-induced reinstatement of cannabinoid-seeking behaviour in male and female rats: influence of ovarian hormones. Br J Pharmacol 160:724-735.

Fehr C, Yakushev I, Hohmann N, Buchholz HG, Landvogt C, Deckers H, Eberhardt A, Klager M, Smolka MN, Scheurich A, Dielentheis T, Schmidt LG, Rosch F (2008) Association of low striatal dopamine D2 receptor availability with nicotine dependence similar to that seen with other drugs of abuse.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Feltenstein MW and See RE (2007) Plasma progesterone levels and cocaine-seeking in freely cycling female rats across the estrous cycle. Drug Alcohol Depend 89:183-189.

Feltenstein MW, Byrd EA, Henderson AR, See RE (2008) Attenuation of cocaine-seeking by progesterone treatment in female rats. Psychoneuroendocrinology 34:343-352.

Fernandez-Montalvo J, Lopez Goni JJ, Azanza P, Cacho R (2014) Gender differences in drug-addicted patients in treatment. The American Journal on Addictions 23:399-406.

Fernandez-Sola, Estruch R, Nicolas JM, Pare JC, Sacanella E, Antunez E, Urbano-Marquez A (1997) Comparison of alcoholic cardiomyopathy in women versus men. The American Journal of Cardiology 80:481-485.

Festa ED, Jenab S, Weiner J, Nazarian A, Niyomchai T, Russo SJ, Kemen LM, Akhavan A, Wu HBK, Quinones-Jenab V (2006) Cocaine-induced sex differences in D1 receptor activation and binding levels after acute cocaine administration. Brain Research Bulletin 68:277-284.

Fiad TM, Cunningham SK, and McKenna TJ (1996) Role of progesterone deficiency in the development of luteinizing hormone and androgen abnormalities in polycystic ovary syndrome. European Journal of Endocrinology 135:335-339.

Fischer KD, Houston ACW, and Rebec GV (2013) Role of the Major Glutamate Transporter GLT1 in Nucleus Accumbens Core Versus Shell in Cue-Induced Cocaine-Seeking Behavior. Journal of Neuroscience 29 33:9314-9327.

Fitch T and Roberts D (1993) The effects of dose and access restrictions on the periodicity of cocaine self-administration in the rat. Drug and Alcohol Dependence 33:119—128

Flores RJ, Pipkin JA, Uribe KP, Perez A, and O'Dell LE (2016) Estradiol promotes the rewarding effects of nicotine in female rats. Behavioural Brain Research 307:258-263.

Fogel JS, Kelly TH, Westgate PM, Lile JA (2017) Sex differences in the subjective effects of oral Δ9-THC in cannabis users. Pharmacol Biochem Behav 152:44-51.

Ford MM, Eldridge JC, and Samson HH (2002) Ethanol consumption in the female Long-Evans rat: a modulatory role of estradiol. Alcohol 26:103-113.

Ford MM, Eldridge JC, Samson HH (2004) Determination of an estradiol dose-response relationship in the modulation of ethanol intake. Alcoholism: Clinical and Experimental Research 28:20-28.

Forger NG and Morin LP (1982) Reproductive state modulates ethanol intake in rats: effects of ovariectomy, ethanol concentration, estrous cycle and pregnancy. Pharmacology, Biochemistry and Behavior 17:323-331.

Forlano PM and Woolley CS (2010) Quantitative analysis of pre- and postsynaptic sex differences in the nucleus accumbens. J Comp Neurol 518:1330-1348.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Fox HC, Hong KA, Paliwal P, Morgan PT, and Sinha R (2007) Altered levels of sex and stress steroid hormones assessed daily over a 28-day cycle in early abstinent cocaine-dependent females. Psychopharmacology 195:527-536.

Fox HC, Sofuoglu M, Morgan PT, Tuit KL, and Sinha R (2013) The effects of exogenous progesterone on drug craving and stress arousal in cocaine dependence: impact of gender and cue type. Psychoneuroendocrinology 38:1532-1544.

Frye CA and Rhodes ME (2006) Administration of estrogen to ovariectomized rats promotes conditioned place preference and produces moderate levels of estrogen in the nucleus accumbens. Brain Research 1067:209-215.

Funk D, Coen K, Tamadon S, Hope BT, Shaham Y, Le AD (2016) Role of central amygdala neuronal ensembles in incubation of nicotine craving. J Neurosci 36:8612-8623.

Gallo MA and Smith SS (1993) Progesterone withdrawal decreases latency to and increases duration of electrified prod burial: a possible rat model of PMS anxiety. Pharmacology, Biochemistry and Behavior 46:897-904.

Gancarz-Kausch A, Adank D, and Dietz D (2014) Prolonged withdrawal following cocaine self-administration increases resistance to punishment in a cocaine binge. Scientific Reports 4:6876

Gatewood J, Wills A, Shetty S, Xu J, Arnold A, Burgoyne P, and Rissman E (2006) Sex Chromosome Complement and Gonadal Sex Influence Aggressive and Parental Behaviors in Mice. Journal of Neuroscience 26:2335-2342

George BE, Barth SH, Kuiper LB, Holleran KM, Lacy RT, Raab-Graham KF, Jones SR (2021) Enhanced heroin self-administration and distinct dopamine adaptations in female rats. Neuropsychopharmacology 46:1724-1733.

Glaser JH, Rubin BS, Barfield RJ (1983) Onset of the receptive and proceptive components of feminine sexual behavior in rats following the intravenous administration of progesterone. Hormones and Behavior 17:18-27.

Goldstein RZ and Volkow ND (2011) Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. Nat Rev Neurosci 12:652-669.

Goldstein RZ, Volkow ND. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. Nature reviews neuroscience. 2011;12:652.

Goletiani NV, Siegel AJ, Lukas SE, and Hudson JI (2015) The effects of smoked nicotine on measures of subjective states and hypothalamic-pituitary-adrenal axis hormones in women during the follicular and luteal phases of the menstrual cycle. J Addict Med 9:195-203.

Grant JE, Odlaug BL, and Mooney ME (2012) Telescoping phenomenon in pathological gambling: association with gender and comorbidities. The Journal of Nervous and Mental Disease 200:996-998.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Greenfield SF, Back SE, Lawson K, Brady KT (2010) Substance abuse in women. Psychiatr Clin North Am 33:339-355.

Greenfield SF, Brooks AJ, Gordon SM, Green CA, Kropp F, McHugh RK, Lincoln M, Hien D, Miele GM (2007) Substance abuse treatment entry, retention, and outcome in women: a review of the literature. Drug Alcohol Depend 86:1-21.

Gresch PJ, Sved AF, Zigmond MJ, and Finlay JM (1994) Stress-induced sensitization of dopamine and norepinephrine efflux in medial prefrontal cortex of the rat. Journal of Neurochemistry 63:575-583.

Griffin ML, Weiss RD, Mirin SM, and Lange U (1989) A comparison of male and female cocaine abusers. The Archives of General Psychiatry 46:122-126.

Grusser SM, Erase J, Klein S, Hermann D, Smolka MN, Ruf M, Weber-Fahr W, Flor H, Mann K, Braus DF, Heinz A (2004) Cue-induced activation of the striatum and medial prefrontal cortex is associated with subsequent relapse in abstinent alcoholics. Psychopharmacology 175:296-302.

Haas AL and Peters RH (2000) Development of substance abuse problems among drug-involved offenders: evidence for the telescoping effect. Journal of Substance Abuse 12:241-253.

Hafenbriedel M, Todd CR, Mueller D (2017) Infralimbic GluN2A-containing NMDA receptors modulate reconsolidation of cocaine self-administration memory. Neuropsychopharmacology 42:1113-1125.

Hansen MS, Licaj I, Braaten T, Langhammer A, Le Marchand L, Gram IT (2018) Sex differences in risk of smoking-associated lung cancer: results from a cohort of 600,000 Norwegians. American Journal of Epidemiology 187:971-981.

Hanzal N, Joyce KM, Tibbo PG, and Stewart SH (2019) A pilot daily diary study of changes in stress and cannabis use quantity across the menstrual cycle. Cannabis 2:120-134.

Hearing M, Graziane N, Dong Y, Thomas MJ (2018) Opioid and psychostimulant plasticity: targeting overlap in nucleus accumbens glutamate signaling. Trends in Pharmacological Sciences 39:276-294.

Hecht GS, Spear NE, and Spear LP (1999) Changes in progressive ratio responding for intravenous cocaine throughout the reproductive process in female rats. Developmental Psychobiology 35:136-145.

Hemby S, Tang W, Muly E, Kuhar M, Howell L, and Mash D (2005) Cocaine-induced alterations in nucleus accumbens ionotropic glutamate receptor subunits in human and non-human primates. Journal of Neurochemistry 95:1785–1793

Hernandez-Avila CA, Rounsaville BJ, and Kranzler HR (2004) Opioid-, cannabis- and alcohol-dependent women show more rapid progression to substance abuse treatment. Drug and Alcohol Dependence 74:265-272.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Herzog AG (1995) Progesterone therapy in women with complex partial and secondary generalized seizures. Neurology 45:1660-1662.

Hesselbrock MN, Meyer RE, and Keene JJ (1985) Psychopathology in hospitalized alcoholics. Archives of General Psychiatry 42:1050-1055.

Hilderbrand ER and Lasek AW (2018) Estradiol enhances ethanol reward in female mice through activation of ERα and ERβ. Hormones and Behavior 98:159-164.

Hinderaker K, Allen AM, Tosun N, al'Absi M, Hatsukami D, and Allen SS (2015) The effect of combination oral contraceptives on smoking-related symptomatology during short-term smoking abstinence. Addict Behav 41:148-151.

Hommer D, Momenan R, Kaiser E, Rawlings RR (2001) Evidence for a gender-related effect of alcoholism on brain volumes. Am J Psychiatry 158:198-204.

Hommer D, Momenan R, Rawlings R (1996) Decreased corpus callosum size among alcoholic women. Arch Neurol 53:359-363.

Hser YI, Anglin MD, and Booth MW (1987) Sex differences in addict careers. 3. addiction. American Journal of Drug and Alcohol Abuse 13:231-251.

Hu M and Becker JB (2003) Effects of sex and estrogen on behavioral sensitization to cocaine in rats. Journal of Neuroscience 23:693-699.

Hu M and Becker JB (2008) Acquisition of cocaine self-administration in ovariectomized female rats: effect of estradiol dose or chronic estradiol administration. Drug and Alcohol Dependence 94:56-62.

Hugues JN, Coste T, Perret G, Jayle MF, Sebaoun J, and Modigliani E (1980) Hypothalamo-pituitary ovarian function in thirty-one women with chronic alcoholism. Clinical Endocrinology 12:543-551.

Ibanez A, Blanco C, Moreryra P, and Saiz-Ruiz J (2003) Gender differences in pathological gambling. The Journal of Clinical Psychiatry 64:295-301.

Imperato A, Puglisi-Allegra S, Casolini P, Zocchi A, and Angelucci L (1989) Stress-induced enhancement of dopamine and acetylcholine release in limbic structures: role of corticosterone. Eur J Pharmacol 165:337-338

Itoh Y, Mackie R, Kampf K, Domadia S, Brown J, O'Neill, and Arnold A (2015) Four Core Genotypes mouse model: localization of the Sry transgene and bioassay for testicular hormone levels. BMC Research Notes 8:69

Iversen J, Wand H, Gonnermann A, and Maher L (2010) Gender differences in hepatitis C antibody prevalence and risk behaviors amongst people who inject drugs in Australia 1998-2008. International Journal of Drug Policy 21:471-476.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Jackson LR, Robinson TE, and Becker BE (2006) Sex differences and hormonal influences on acquisition of cocaine self-administration in rats. Neuropsychopharmacology 31:129-138.

Jandikova H, Duskova M, and Starka L (2017) The influence of smoking and cessation on the human reproductive hormonal balance. Physiological Research 66:323-331.

Johnson AR, Thibeault KC, Lopez AJ, Peck EG, Sands LP, Sanders CM, Kutlu MG, Calipari ES (2019) Cues play a critical role in estrous cycle-dependent enhancement of cocaine reinforcement. Neuropsychopharmacology 44:1189-1197.

Johnson PB, Richter L, Kleber HD, McLellan AT, and Carise D (2005) Telescoping of drinking-related behaviors: gender, racial/ethnic, and age comparisons. Substance Use & Misuse 40:1139-1151.

Joseph, J. E., McRae-Clark, A., Sherman, B. J., Baker, N. L., Maria, M. S., & Brady, K. T. (2019). Neural correlates of oxytocin and cue reactivity in cocaine-dependent men and women with and without childhood trauma. Psychopharmacology, 1-13.

Joyce KM, Good KP, Tibbo P, Brown J, and Stewart SH (2021) Addictive behaviors across the menstrual cycle: a systematic review. Archives of Women's Mental Health 24:529-542.

Joyce KM, Hudson A, O'Connor R, Thompson K, Hodgin M, Perrot T, Stewart SH (2018) Changes in coping and social motives for drinking and alcohol consumption across the menstrual cycle. Depression and Anxiety 35:313-320.

Justice AJH and de Wit H (2000) Acute effects of d-amphetamine during the early and late follicular phases of the menstrual cycle in women. Pharmacology, Biochemistry and Behavior 66:509-515.

Kalivas P and McFarland K (2003) Brain circuitry and the reinstatement of cocaine-seeking behavior. Psychopharmacology 168:44–56

Kalivas P and Volkow N (2005) The Neural Basis of Addiction: A Pathology of Motivation and Choice. American Journal of Psychiatry 162:1403-1413

Kalivas P and Volkow N (2011) New medications for drug addiction hiding in glutamatergic neuroplasticity. Molecular Psychiatry 16:974–986

Kampman KM, Pettinati H, Lynch KG, Dackis C, Sparkman T, Weigley C, and O'Brien CP (2004) A pilot trial of topiramate for the treatment of cocaine dependence. Drug and Alcohol Dependence 75:233-240

Kaplan JR and Manuck SB (2004) Ovarian dysfunction, stress, and disease: a primate continuum. ILAR J 45:89-115.

Kawa A and Robinson T (2019) Sex differences in incentive-sensitization produced by intermittent access cocaine self-administration. Psychopharmacology 236:625—639

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Kendler KS, Ohlsson H, Svikis DS, Sundquist K, Sundquist J (2017) The protective effect of pregnancy on risk for drug abuse: a population, co-relative, co-spouse, and within-individual analysis. Am J Psychiatry 174:954-962.

Kerstetter K, Ballis M, Duffin-Lutgen S, Carr A, Behrens A, and Kippin T (2012) Sex Differences in Selecting Between Food and Cocaine Reinforcement are Mediated by Estrogen. Neuropsychopharmacology 37:2605—2614

Kerstetter, K. A., Aguilar, V. R., Parrish, A. B., & Kippin, T. E. (2008). Protracted time-dependent increases in cocaine-seeking behavior during cocaine withdrawal in female relative to male rats. Psychopharmacology, 198(1), 63-75

Keyes KM, Martins SS, Blanco C, and Hasin DS (2010) Telescoping and gender differences in alcohol dependence: new evidence from two national surveys. Am J Psychiatry 167:969-976.

Khan SS, Secades-Villa R, Okuda M, Wang S, Perez-Fuentes G, Kerridge BT, and Blanco C (2013) Gender differences in cannabis use disorders: results from the national epidemic survey of alcohol and related conditions. Drug Alcohol Depend 130:101-108.

Kiesner J (2012) Affective response to the menstrual cycle as a predictor of self-reported affective response to alcohol and alcohol use. Arch Womens Ment Health 15:423-432.

Kilts CD, Kennedy A, Elton AL, Tripathi SP, Young J, Cisler JM, James GA (2014) Individual differences in attentional bias associated with cocaine dependence are related to varying engagement of neural processing networks. Neuropsychopharmacology 39:1135-1147.

Kiyohara C, Ohno Y (2010) Sex differences in lung cancer susceptibility: a review. Gender Medicine 7:381-401.

Knackstedt L and Kalivas P (2009) Glutamate and reinstatement. Current Opinion in Pharmacology 9:59-64

Kokane SS and Perrotti LI (2020) Sex differences and the role of estradiol in mesolimbic reward circuits and vulnerability to cocaine and opiate addiction. Front Behav Neurosci doi:10.3389/fnbeh.2020.00074.

Koob, G. F, Volkow, N. D. (2010). Neurocircuitry of addiction. Neuropsychopharmacology, 35(1), 217-238.

Koob G, Volkow N (2016) Neurobiology of addiction: a neurocircuitry analysis. The Lancet Psychiatry 3:760-773

Koob GF (2021) Drug addiction: hyperkatifeia/negative reinforcement as a framework for medications development. Pharmacological Reviews 73:163-201

Kucerova J, Vrskova D, and Sulcova A (2009) Impact of repeated methamphetamine pretreatment on intravenous self-administration of the drug in males and estrogenized or non-estrogenized ovariectomized female rats. Neuroendocrinology Letters 30:663-670.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Kuhn C, Francis R (1997) Gender difference in cocaine-induced HPA axis activation. Neuropsychopharmacology, 16(6), 399-407.

Kuntz KL, Patel KM, Grigson PS, Freeman WM, Vrana KE (2008) Heroin self-administration: II. CNS gene expression following withdrawal and cue-induced drug-seeking behavior. Pharmacol Biochem Behav 90:349-356.

Kuntz-Melcavage KL, Brucklacher RM, Grigson PS, Freeman WM, Vrana KE (2009) Gene expression changes following extinction testing in a heroin behavioral incubation model. BMC Neurosci doi:10.1186/1471-2202-10-95.

Lacy RT, Strickland JC, Feinstein MA, Robinson AM, and Smith MA (2016) The effects of sex, estrous cycle, and social contact on cocaine and heroin self-administration in rats. Psychopharmacology 233:3201-3210.

Ladd GT and Petry NM (2002) Gender differences among pathological gamblers seeking treatment. Experimental and Clinical Psychopharmacology 10:302-309.

LaLumiere RT and Kalivas PW (2008) Glutamate release in the nucleus accumbens core is necessary for heroin seeking. J Neurosci 28:3170-1377.

Large M, Sharma S, Compton MT, Slade T, and Nielssen O (2011) Cannabis use and earlier onset of psychosis: a systematic meta-analysis. Arch Gen Psychiatry 68:555-561.

Larson EB, Anker JJ, Gliddon LA, Fons KS, and Carroll ME (2007) Effects of estrogen and progesterone on the escalation of cocaine self-administration in female rats during extended access. Experimental and Clinical Psychology 15:461-471.

Lee JY, Ko YJ, Park SM (2013) Factors associated with current smoking and heavy alcohol consumption among women of reproductive age: the Fourth Korean National Health and Nutrition Examination Survey 2007–2009. Public Health. 127(5):473–481.

LeSage MG, Keyler DE, Burroughs D, and Pentel PR (2007) Effects of pregnancy on nicotine self-administration and nicotine pharmacokinetics in rats. Psychopharmacology 194:413-421.

Lewis B and Nixon SJ (2014) Characterizing gender differences in treatment seekers. Alcohol Clin Exp Res 38:275-284.

Lewis B, Hoffman LA, and Nixon SJ (2014) Sex differences in drug use among polysubstance users. Drug Alcohol Depend 145:127-133.

Li C, Dang J, Zhang X, Zhang Q, and Guo J (2014) Internet addiction among Chinese adolescents: The effect of parental behavior and self-control. Computers in Human Behavior 41:1—7

Li X, Caprioli D, Marchant NJ (2015) Recent updates on incubation of drug craving: a mini-review. Addiction Biology 20.5:872-876.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Li, C. S. R., Kosten, T. R., & Sinha, R. (2005). Sex differences in brain activation during stress imagery in abstinent cocaine users: a functional magnetic resonance imaging study. Biological psychiatry, 57(5), 487-494.

Liechti ME, Gamma A, Vollenweider FX (2001) Gender differences in the subjective effects of MDMA. Psychopharmacology 154:161-168.

Lile JA, Kendall SL, Babalonis S, Martin CA, and Kelly TH (2007) Evaluation of estradiol administration on the discriminative-stimulus and subject-rated effects of d-amphetamine in healthy pre-menopausal women. Pharmacology, Biochemistry and Behavior 87:258-266.

Loft S, Olesen KL, Dossing M (1987) Increased susceptibility to liver disease in relation to alcohol consumption in women. Scandinavian Journal of Gastroenterology 22:1251-1256.

Lopez-Quintero C, de los Cobos JP, Hasin DS, Okuda M, Wang S, Grant BF, Blanco C (2011) Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: results of the national epidemiologic survey on alcohol and related conditions (NESARC). Drug Alcohol Depend 115:120-130.

Lovell-Badge and Robertson (1990) XY female mice resulting from a heritable mutation in the primary testis-determining gene, Tdy. Development 109: 635–646

Lukas SE, Sholar M, Lundahl LH, Lamas X, Kouri E, Wines JD, Kragie L, and Mendelson JH (1996) Sex differences in plasma cocaine levels and subjective effects after acute cocaine administration in human volunteers. Psychopharmacology 125:346-354.

Lund E and Jacobsen BK (1990) Use of oral contraceptives in relation to dietary habits and alcohol consumption. Contraception 42:171-177.

Lynch W (2006) Sex differences in vulnerability to drug self-administration. Experimental and Clinical Psychopharmacology 14:34—41

Lynch W (2008) Acquisition and maintenance of cocaine self-administration in adolescent rats: effects of sex and gonadal hormones. Psychopharmacology 197:237—246

Lynch W (2018) Modeling the development of drug addiction in male and female animals. Pharmacology Biochemistry and Behavior 164:50—61

Lynch W and Carroll M (2001) Regulation of drug intake. Experimental and Clinical Psychopharmacology 9:131—143

Lynch W and Taylor J (2004) Sex differences in the behavioral effects of 24-h/day access to cocaine under a discrete trial procedure. Neuropsychopharmacology 29:943—951

Lynch W and Taylor J (2005) Decreased motivation following cocaine self-administration under extended access conditions: effects of sex and ovarian hormones. Neuropsychopharmacology 30:927—935

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Lynch W, Nicholson K, Dance M, Morgan R, and Foley P (2010) Animal Models of Substance Abuse and Addiction: Implications for Science, Animal Welfare, and Society. Comparative Medicine 6:177—188

Lynch WJ (2008) Acquisition and maintenance of cocaine self-administration in adolescent rats: effects of sex and gonadal hormones. Psychopharmacology 197:237-246.

Lynch WJ (2009) Sex and ovarian hormones influence vulnerability and motivation for nicotine during adolescence in rats. Pharmacology, Biochemistry and Behavior 94:43-50.

Lynch WJ, Arizzi MN, and Carroll ME (2000) Effects of sex and the estrous cycle of regulation of intravenously self-administered cocaine in rats. Psychopharmacology 152:132-139.

Lynch WJ, Kalayasiri R, Sughondhabirom A, Pittman B, Coric V, Morgan PT, Malison RT (2008) Subjective responses and cardiovascular effects of self-administered cocaine in cocaine-abusing men and women. Addict Biol 13:403-410.

Lynch WJ, Kiraly DD, Calderone BJ, Picciotto MR, Taylor JR (2007) Effect of cocaine self-administration on striatal PKA-regulated signaling in male and female rats. Psychopharmacology 191:263-271.

Lynch WJ, Roth ME, Carroll ME (2002) Biological basis of sex differences in drug abuse: preclinical and clinical studies. Psychopharmacology 164:121-137.

Mackay L, Ickowicz S, Hayashi K, Abrahams R (2020) Rooming-in and loss of child custody: key factors in maternal overdose risk. Addiction 115:1786-1787.

Maher EE, Kipp ZA, Leyrer-Jackson JM, Khatri S, Bondy E, Martinez GJ, Beckmann JS, Hinds, Jr. TD, Bimonte-Nelson HA, Gipson CD (2022) Ovarian hormones regulate nicotine consumption and accumbens glutamatergic plasticity in female rats. eNeuro doi:10.1523/ENEURO.0286-21.2022.

Maldonado R, Robledo P, Chover A, Caine S, Koob G (1993) D1 dopamine receptors in the nucleus accumbens modulate cocaine self-administration in the rat. Pharmacology Biochemistry and Behavior 45:239-242

Mangiavacchi S, Masi F, Scheggi S, Leggio B, De Montis MG, and Gambarana C (2001) Long-term behavioral and neurochemical effects of chronic stress exposure in rats. Journal of Neurochemistry 79:1113-1121.

Mann K, Ackermann K, Croissant B, Mundle G, Nakovics H, and Diehl A (2005) Neuroimaging of gender differences in alcohol dependence: are women more vulnerable? Alcoholism: Clinical and Experimental Research 29:896-901.

Mann K, Batra A, Gunthner A, and Schroth G (1992) Do women develop alcoholic brain damage more readily than men? Alcoholism: Clinical and Experimental Research 16:1052-1056.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Manza P, Shokri-Kojori E, Wiers C, Kroll D, Feldman D, McPherson K,Biesecker E, Dennis E, Johnson A, Kelleher A, et al. (2022) Sex differences in methylphenidate-induced dopamine increases in ventral striatum. Molecular Psychiatry 27:939–946

Marinelli, M., & Piazza, P. V. (2002). Interaction between glucocorticoid hormones, stress and psychostimulant drugs. European Journal of Neuroscience, 16(3), 387-394.

Martin CA, Mainous AG, Curry T, and Martin D (1999) Alcohol use in adolescent females: correlates with estradiol and testosterone. American Journal on Addictions 8:9-14.

Martinez D, Broft A, Foltin RW, Slifstein M, Hwang DR, Huang Y, Perez A, Frankel WG, Cooper T, Kleber HD, Fischman MW, Laruelle M (2004) Cocaine dependence and D2 receptor availability in the functional subdivisions of the striatum: relationship with cocaine-seeking behavior. Neuropsychopharmacology 29:1190-1202.

Martinez D, Carpenter KM, Liu F, Slifstein M, Broft A, Friedman AC, Kumar D, Heertum RV, Kleber HD, Nunes E (2011) Imaging dopamine transmission in cocaine dependence: link between neurochemistry and response to treatment. Am J Psychiatry doi: 10.1176/appi.ajp.2010.10050748.

Martinez D, Gil R, Slifstein M, Hwang DR, Huang Y, Perez A, Kegeles L, Talbot P, Evans S, Krystal J, Laruelle M, Abi-Dargham A (2005) Alcohol dependence is associated with blunted dopamine transmission in the ventral striatum. Biological Psychiatry 58:779-786.

Martinez D, Saccone PA, Liu F, Slifstein M, Orlowska D, Grassetti A, Cook S, Broft A, Heertum RV, Comer SD (2012) Deficits in dopamine D2 receptors and presynaptic dopamine in heroin dependence: commonalities and differences with other types of addiction. Biological Psychiatry 71:192-198.

Martinez LA, Gross KS, Himmler BT, Emmitt NL, Peterson BM, Zlebnik NE, Olive MF, Carroll ME, Meisel RL, Mermelstein PG (2016) Estradiol facilitation of cocaine self-administration in female rats requires activation of mGluR5. eNeuro doi: 10.1523/ENEURO.0140-16.2016.

Martini M, Irvin J, Lee C, Lynch W, and Emilie Rissman (2020) Sex chromosome complement influences vulnerability to cocaine in mice. Hormones and Behavior 125:104821

Matheson J, Sproule B, Ciano P, Fares A, Foll B, Mann R, and Brands B (2020) Sex differences in the acute effects of smoked cannabis: evidence from a human laboratory study of young adults. Psychopharmacology 237:305–316

Mayo LM, Paul E, DeArcangelis J, Hedger KV, de Wit H (2019) Gender differences in the behavioral and subjective effects of methamphetamine in healthy humans. Psychopharmacology 236:2413-2423.

McCance-Katz EF, Carroll KM, and Rounsaville BL (1999) Gender differences in treatment-seeking cocaine abusers--implications for treatment and prognosis. The American Journal on Addictions 8:300-311.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

McGregor A and Roberts D (1993) Dopaminergic antagonism within the nucleus accumbens or the amygdala produces differential effects on intravenous cocaine self-administration under fixed and progressive ratio schedules of reinforcement. Brain Research 624: 245-252

Meaney MJ, Brake W, and Gratton A (2002) Environmental regulation of the development of mesolimbic dopamine systems: a neurobiological mechanism for vulnerability to drug abuse? Psychoneuroendocrinology 27:127-138.

Mello NK, Bree MP, Skupny AS, Mendelson JH (1984) Blood alcohol levels as a function of menstrual cycle phase in female macaque monkeys. Alcohol 1:27-31.

Mello NK, Knudson IM, Kelly M, Fivel PA, Mendelson JH (2011) Effects of progesterone and testosterone on cocaine self-administration and cocaine discrimination by female rhesus monkeys. Neuropsychopharmacology 36:2187-2199.

Mello NK, Knudson IM, Mendelssohn JH (2007) Sex and menstrual cycle effects on progressive ratio measures of cocaine self-administration in cynomolgus monkeys. Neuropsychopharmacology 32:1956-1966.

Mello NK, Mendelson JH, and Lex BW (1990) Alcohol use and premenstrual symptoms in social drinkers. Psychopharmacology 101:448-455.

Melon L, Wray K, Moore E, Boehme-II S (2013) Sex and age differences in heavy binge drinking and its effects on alcohol responsivity following abstinence. Pharmacology Biochemistry and Behavior 104:177—187

Mendelson J, Mello N, Sholar M, Siegel A, Kaufman M, Levin J, Renshaw P, and Cohen B (1999) Cocaine Pharmacokinetics in Men and in Women During the Follicular and Luteal Phases of the Menstrual Cycle. Neuropsychopharmacology 21:294–303

Mihov Y, Treyer V, Akkus F, Toman E, Milos G, Ametamey SM, Johayem A, Hasler G. Metabotropic glutamate receptor 5 in bulimia nervosa. Sci Rep. 2020 Apr 14;10(1):6374. doi: 10.1038/s41598-020-63389-7.

Mirbaha H, Tabaeizadeh M, Shaterian-Mohammadi H, Tahsili-Fahadan P, and Dehpour AR (2009) Estrogen pretreatment modulates morphine-induced conditioned place preference in ovariectomized mice. Pharmacology, Biochemistry and Behavior 92:399-403.

Mishra D, Pena-Bravo JI, Leong KC, Lavin A, Reichel CM (2017) Methamphetamine self-administration modulates glutamate neurophysiology. Brain Struct Funct 222:2031-2039.

Moore C and Lynch W (2015) Alcohol preferring (P) rats as a model for examining sex differences in alcohol use disorder and its treatment. Pharmacology Biochemistry and Behavior 132:1—9

Moran MH, Goldberg M, and Smith SS (1998) Progesterone withdrawal: II: insensitivity to the sedative effects of benzodiazepine. Brain Research 807:91-100.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Morgan D, Grant KA, Gage HD, Mach RH, Kaplan JR, Prioleau O, Nader SH, Buchheimer N, Ehrenkaufer RL, Nader MA (2002) Social dominance in monkeys: dopamine D2 receptors and cocaine self-administration. Nat Neurosci 5(2):169-74.

Munro C, McCaul M, Wong D, Oswald L, Zhou Y, Brasic J, Kuwabara H, Kumar A, Mohab A, Ye W, et al. (2006) Sex Differences in Striatal Dopamine Release in Healthy Adults. Biological Psychiatry 59:966-974

Murray CH, Christian DT, Milovanovic M, Loweth JA, Hwang EK, Caccamise AJ, Funke JR, Wolf ME (2021) mGlu5 function in the nucleus accumbens core during the incubation of methamphetamine craving. Neuropharmacology doi:10.1016/j.neuropharm.2021.108452.

Nader MA, Nader SH, Czoty PW, Riddick NV, Gage HD, Gould RW, Blaylock BL, Kaplan JR, Garg PK, Davies HM, Morton D (2012) Social dominance in female monkeys: dopamine receptor function and cocaine reinforcement. Biological psychiatry 72(5):414-21.

Nicolaides BM (1996) The state's 'sharp line between the sexes': women, alcohol and the law in the United States, 1850-1890. Addiction 91:1211-1229.

Nicolas C, Russell TI, Pierce AF, Maldera S, Holley A, You ZB, McCarthy MM, Shaham Y, and Ikemoto S (2019) Incubation of cocaine craving after intermittent-access self-administration: sex differences and estrous cycle. Biological Psychiatry 85:915-924.

O'Brien MS, Anthony JC (2005) Risk of becoming cocaine dependent: epidemiological estimates for the United States, 2000-2001. Neuropsychopharmacology 30:1006-1018

Okita K, Peterson N, Robertson CL, Dean AC, Mandelkern MA, London ED (2016) Sex differences in midbrain dopamine D2-type receptor availability and association with nicotine dependence. Neuropsychopharmacology 41:2913-2919.

Origer A, Le Bihan E, Baumann M (2014) Social and economic inequalities in fatal opioid and cocaine related overdoses in Luxembourg: a case-control study. International Journal of Drug Policy 25:911-915.

Oswald L, Wand G, Wong D, Brown C, Kuwabara H, and Brašić J (2015) Risky decision-making and ventral striatal dopamine responses to amphetamine: A positron emission tomography [11C]raclopride study in healthy adults. NeuroImage 113:26-36

Oswald, L. M., Wand, G. S., Kuwabara, H., Wong, D. F., Zhu, S., & Brasic, J. R. (2014). History of childhood adversity is positively associated with ventral striatal dopamine responses to amphetamine. Psychopharmacology, 231(12), 2417-2433.

Pacak, K., Tjurmina, O., Palkovits, M., Goldstein, D. S., Koch, C. A., Hoff, T., & Chrousos, G. P. (2002). Chronic hypercortisolemia inhibits dopamine synthesis and turnover in the nucleus accumbens: an in vivo microdialysis study. Neuroendocrinology, 76(3), 148-157

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Pacchioni A, Gabriele A, and See R (2011) Dorsal striatum mediation of cocaine-seeking after withdrawal from short or long daily access cocaine self-administration in rats. Behavioral Brain Research 2:296—300

Patrat C, Ouimette JF, and Rougeulle C (2020) X chromosome inactivation in human development. Development 147

Peltier MR and Sofuoglu M (2018) The role of exogenous progesterone in the treatment of males and females with substance use disorders: a narrative review. CNS Drugs 32:421-435.

Peltier MR, Sofuoglu M, Petrakis IL, Stefanovics E, and Rosenheck RA (2021) Sex differences in opioid use disorder prevalence and multimorbidity nationally in the Veterans Health Administration. Journal of Dual Diagnosis 17:124-134.

Pena-Bravo JI, Penrod R, Reichel CM, Lavin A (2019) Methamphetamine self-administration elicits sex-related changes in postsynaptic glutamate transmission in the prefrontal cortex. eNeuro doi:10.1523/ENEURO.0401-18.2018.

Perkins KA (1999) Nicotine discrimination in men and women. Pharmacol Biochem Behav 64:295–299

Perkins KA, Levine M, Marcus M, Shiffman S, D'Amico D, Miller A, Keins A, Ashcom J, and Broge M (2000) Tobacco withdrawal in women and menstrual cycle phase. Journal of Consulting and Clinical Psychology 68:176-180.

Perry A, Westenbroek C, Jagannathan L, and Becker J (2015) The Roles of Dopamine and α1-Adrenergic Receptors in Cocaine Preferences in Female and Male Rats. Neuropsychopharmacology 40:2696—2704

Perry AN, Westenbroek C, and Becker JB (2013) Impact of pubertal and adult estradiol treatments on cocaine self-administration. Hormones and Behavior 64:573-578.

Peters J, LaLumiere R, and Kalivas P (2008) Infralimbic Prefrontal Cortex Is Responsible for Inhibiting Cocaine Seeking in Extinguished Rats. Journal of Neuroscience 28:6046-6053

Peterson BM, Mermelstein PG, Meisel RL (2015) Estradiol mediates dendritic spine plasticity in the nucleus accumbens core through activation of mGluR5. Brain Struct Funct 220:2415-2422.

Piazza NJ, Vrbka JL, and Yeager RD (1989) Telescoping of alcoholism in women alcoholics. International Journal of the Addictions 24:19-28.

Piazza PV, Deroche V, Deminiere JM, Maccari S, Moal ML, and Simon H (1993) Corticosterone in the range of stress-induced levels possesses reinforcing properties: implications for sensation-seeking behaviors. Proc Natl Acad Sci USA 90:11738-11742.

Piazza, P. V., & Le Moal, M. (1997). Glucocorticoids as a biological substrate of reward: physiological and pathophysiological implications. Brain Research Reviews, 25(3), 359-372.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Piazza, Pier Vincenzo, and Michel Le Moal. "Pathophysiological basis of vulnerability to drug abuse: role of an interaction between stress, glucocorticoids, and dopaminergic neurons." Annual review of pharmacology and toxicology 36.1 (1996): 359-378

Pickens CL, Airavaara M, Theberge F, Fanous S, Hope BT, Shaham Y (2011) Neurobiology of the incubation of drug craving. Trends Neurosci 34:411-420.

Pierce C and Kumaresan V (2006) The mesolimbic dopamine system: The final common pathway for the reinforcing effect of drugs of abuse. Neuroscience & Biobehavioral Reviews 30:215-238

Poole N and Isaac B (2001) Barriers to treatment for substance-using mothers. British Columbia Centre of Excellence for Women's Health, British Columbia.

Potenza MN, Hong KA, Lacadie CM, Fulbright RK, Tuit KL, Sinha R (2012) Neural correlates of stress-induced and cue-induced drug craving: influences of sex and cocaine dependence. Am J Psychiatry 169:406-414.

Priddy BM, Carmack SA, Thomas LC, Vendruscolo JCM, Koob GF, and Vendruscolo LF (2017) Sex, strain, and estrous cycle influences on alcohol drinking in rats. Pharmacology, Biochemistry and Behavior 152:61-67.

Puetz VB, McCrory E (2015) Exploring the relationship between childhood maltreatment and addiction: a review of the neurocognitive evidence. Curr Addict Rep 2:318-325.

Purgianto A, Scheyer AF, Loweth JA, Ford KA, Tseng KY, Wolf ME (2013) Different adaptations in AMPA receptor transmission in the nucleus accumbens after short vs long access cocaine self-administration regimes. Neuropsychopharmacology 38:1789-1797.

Quinn J, Hitchcott P, Umeda E, Arnold A, and Taylor J (2007) Sex chromosome complement regulates habit formation. Nature Neuroscience 10:1398–1400

Quintero G (2013) Role of nucleus accumbens glutamatergic plasticity in drug addiction. Neuropsychiatr Dis Treat. 9:1499–1512

Rajasingh J, Bord E, Qin G, Li M, Silver M, Hamada H, Ahluwalia D, Goukassian D, Zhu Y, Losordo DW, and Kishore R (2007) Enhanced voluntary alcohol consumption after estrogen supplementation negates estrogen-mediated vascular repair in ovariectomized mice. Endocrinology 148:3618-3624.

Ramoa C, Doyle S, Lycas M, Chernau A, and Lynch W (2014) Diminished role of dopamine D1-receptor signaling with the development of an addicted phenotype in rats. Biol Psychiatry 76:2—3

Ramoa C, Doyle S, Naim D, and Lynch W (2013) Estradiol as a mechanism for sex differences in the development of an addicted phenotype following extended access cocaine self-administration. Neuropsychopharmacology 38:1698—1705

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Randall CL, Roberts JS, Del Boca FK, Carroll KM, Connors GJ, and Mattson ME (1999) Telescoping of landmark events associated with drinking: a gender comparison. Journal of Studies on Alcohol and Drugs 60:252-260.

Recovery of Decreased Metabotropic Glutamate Receptor 5 Availability in Abstinent Alcohol-Dependent Patients. Ceccarini J, Leurquin-Sterk G, Crunelle CL, de Laat B, Bormans G, Peuskens H, Van Laere K. J Nucl Med. 2020 Feb;61(2):256-262. doi: 10.2967/jnumed.119.228825. Epub 2019 Sep 3.

Reichel C, Chan C, Ghee S, and See R (2012) Sex differences in escalation of methamphetamine self-administration: cognitive and motivational consequences in rats. Psychopharmacology 223:371—380

Ribeiro-Dasilva MC, Shinal RM, Glover T, Williams RS, Staud R, Riley, III JL, and Fillingim RB (2011) Evaluation of menstrual cycle effects on morphine and pentazocine analgesia. Pain 152:614-622.

Riccardi P, Li R, Ansari M, Zald D, Park S, Dawant B, Anderson S, Doop M, Woodwafc N, Schoenberg E, et al. (2006) Amphetamine-Induced Displacement of [18F] Fallypride in Striatum and Extrastriatal Regions in Humans. Neuropsychopharmacology 31:1016–1026

Roberts AJ, Smith AD, Weiss SF, Rivier C, Koob GF (1998) Estrous cycle effects on operant responding for ethanol in female rats. Alcoholism: Clinical and Experimental Research 22:1564-1569.

Roberts D, Morgan D, and Liu Y (2007) How to make a rat addicted to cocaine. Neuro Psychopharmacology and Biological Psychiatry 31:1614—1624

Roberts DCS, Bennett SAL, and Vickers GJ (1989) The estrous cycle affects cocaine self-administration on a progressive ratio schedule in rats. Psychopharmacology 98:408-411.

Rogers JL, Ghee S, See RE (2008) The neural circuitry underlying reinstatement of heroin-seeking behavior in an animal model of relapse. Neuroscience 151:579-588.

Roth M and Carroll M (2004) Sex differences in the escalation of intravenous cocaine intake following long- or short-access to cocaine self-administration. 78:199—207

Roth ME, Casimir AG, and Carroll ME (2002) Influence of estrogen in the acquisition of intravenously self-administered heroin in female rats. Pharmacology, Biochemistry and Behavior 72:313-318.

Roura-Martinez D, Diaz-Bejarano P, Ucha M, Paiva RR, Ambrosio E, Higuera-Matas A (2020) Comparative analysis of the modulation of perineuronal nets in the prefrontal cortex of rats during protracted withdrawal from cocaine, heroin and sucrose self-administration. Neuropharmacology doi:10.1016/j.neuropharm.2020.108290.

Rubio FJ, Quintana-Feliciano R, Warren BL, Li X, Witonsky KFR, Soto del Valle F, Selvam PV, Caprioli D, Venniro M, Bossert JM, Shaham Y, Hope BT (2019) Prelimbic cortex is a

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

common brain area activated during cue-induced reinstatement of cocaine and heroin seeking in a polydrug self-administration rat model. Eur J Neurosci 49:165-178.

Russo SJ, Sun WL, Minerly ACE, Weierstall K, Nazarian A, Festa ED, Niyomchai T, Akhavan A, Luine V, Jenab S, and Quinones-Jenab V (2008) Progesterone attenuates cocaine-induced conditioned place preference in female rats. Brain Research 1189:229-235.

Sanchez V, Moore CF, Brinzell DH, Lynch WJ (2014) Sex differences in the effect of wheel running on subsequent nicotine-seeking in a rat adolescent-onset self-administration model. Psychopharmacology (Berl) 231:1753-1762.

Schmidt H and Pierce C (2010) Cocaine-induced neuroadaptations in glutamate transmission: potential therapeutic targets for craving and addiction. Addiction Reviews 2 1187:35-75

Schmidt HD, Anderson SM, Famous KR, Kumaresan V, Pierce RC (2005) Anatomy and pharmacology of cocaine priming-induced reinstatement of drug seeking. Eur J Pharmacology 526:65-76.

Schmidt KT, Sharp JL, Ethridge SB, Pearson T, Ballard S, Potter KM, and Smith MA (2021) The effects of strain and estrous cycle on heroin- and sugar-maintained responding in female rats. Behavioural Brain Research 409:113329.

Schuckher F, Sellin T, Fahlke C, Engstrom I (2018) The impact of childhood maltreatment on age of onset of alcohol use disorder in women. Eur Addict Res 24:278-285.

Schuckit MA, Anthenelli RM, Bucholz KK, and Hes VM (1995) The time course of development of alcohol-related problems in men and women. Journal of Studies on Alcohol 56:218-225.

Scragg R, Wellman RJ, Laugesen M, DiFranza JR (2008) Diminished autonomy over tobacco can appear with the first cigarettes. Addictive Behaviors 33:689-698.

Seo D, Jia Z, Lacadie CM, Tsou KA, Bergquist K, Sinha R (2011) Sex differences in neural responses to stress and alcohol context cues. Hum Brain Mapp 32:1998-2013.

Shams W, Cossette MP, Shizgal P, and Brake W (2018) 17β-estradiol locally increases phasic dopamine release in the dorsal striatum. Neuroscience Letters 665:29-32

Shams WM, Sanio C, Quinlan MG, Brake WG (2016) 17β-estradiol infusions into the dorsal striatum rapidly increase dorsal striatal dopamine release in vivo. Neuroscience 330:162-170.

Shantha K. Mahadevaiah S, Odorisio T, Elliott D, Rattigan A, Szot M, Laval S,Washburn L, McCarrey J, Cattanach B, Lovell-Badge R et al. (1998) Mouse Homologues of the Human AZF Candidate Gene RBM Are Expressed in Spermatogonia and Spermatids, and Map to a Y Chromosome Deletion Interval Associated with a High Incidence of Sperm Abnormalities. Molecular Genetics 7:715—727

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Sharp JL, Ethridge SB, Ballard SL, Potter KM, Schmidt KT, and Smith MA (2021) The effects of chronic estradiol treatment on opioid self-administration in intact female rats. Drug and Alcohol Dependence 225:108816.

Shen H, Moussawi K, Zhou W, Toda S, Kalivas PW. Heroin relapse requires long-term potentiation-like plasticity mediated by NMDA2b-containing receptors. Proceedings of the National Academy of Sciences of the United States of America. 2011;108:19407-19412.

Sherman BJ, Caruso MA, and McRae-Clark AL (2019) Exogenous progesterone for cannabis withdrawal in women: feasibility trial of a novel multimodal methodology. Pharmacology, Biochemistry and Behavior 179:22-26.

Shin CB, Templeton TJ, Chiu AS, Kim J, Gable ES, Vieira PA, Kippin TE, Szumlinski KK (2018) Endogenous glutamate within the prelimbic and infralimbic cortices regulates the incubation of cocaine-seeking in rats. Neuropharmacology 128:293-300.

Siemsen BM, Giannotti G, McFadden JA, Scofield MD, McGinty JF (2019) Biphasic effect of abstinence duration following cocaine self-administration on spine morphology and plasticity-related proteins in prelimbic cortical neurons projecting to the nucleus accumbens core. Brain Struct Funct 224:741-758.

Silverman JL, and Koenig JI (2007) Evidence for involvement of ERβ and RGS9-2 in 17-β estradiol enhancement of amphetamine-induced place preference behavior. Hormones and Behavior 52:146-155.

Sinha R (2001) How does stress increase risk of drug abuse and relapse? Psychopharmacology 158:343-359.

Sinha R (2008) Chronic stress, drug use, and vulnerability to addiction. Ann N Y Acad Sci 1141:105-130.

Sinha R, Fox H, Kong KI, Sofuoglu M, Morgan PT, and Bergquist KT (2007) Sex steroid hormones, stress response, and drug craving in cocaine-dependent women: implications for relapse susceptibility. Experimental and Clinical Psychopharmacology 15:445-452.

Sinha R, Garcia M, Paliwal P, Kreek MJ, and Rounsaville BJ (2006) Stress-induced cocaine craving and hypothalamic-pituitary-adrenal responses are predictive of cocaine relapse outcomes. Arch Gen Psychiatry 63:324-331.

Slutske WS, Piasecki TM, Deutsch AR, Statham DJ, and Martin NG (2015) Telescoping and gender differences in the time course of disordered gambling: evidence from a general population sample. Addiction 110:144-151.

Small CM, Manatunga AK, Marcus M (2007) Validity of self-reported menstrual cycle length. Annals of Epidemiology 17:163-170.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Smethells JR, Swalve NL, Eberly LE, and Carroll ME (2016) Sex differences in the reduction of impulsive choice (delay discounting) for cocaine in rats with atomoxetine and progesterone. Psychopharmacology 233:2999-3008.

Smith C, Dang L, Burgess L, Perkins S, Juan D, Smith D, Cowan R, Le N, Kessler R, Samanez-Larkin G, et al. (2019) Lack of consistent sex differences in D-amphetamine-induced dopamine release measured with [18F]fallypride PET. Psychopharmacology 236:581–590

Smith M, Walker K, Cole K, and Lang K (2011) The effects of aerobic exercise on cocaine self-administration in male and female rats. Psychopharmacology 218:357

Smith MA, Ethridge SB, Pearson T, Zhang H, Marcus MM, Ballard SL, Casimir AT, Potter KM, Schmidt KT, Sharp JL, and Robinson AM (2021) Modulation of heroin intake by ovarian hormones in gonadectomized and intact female rats. Psychopharmacology 238:969-978.

Smith SS, Gong QH, Hsu FC, Markowitz RS, ffrench-Mullen JM, and Li X (1998) GABA(A) receptor alpha4 subunit suppression prevents withdrawal properties of an endogenous steroid. Nature 392:926-930.

Smith-Bouvier D, Divekar A, Sasidhar M, Du S, Tiwari-Woodruff S, King J, Arnold A, Singh R, and Voskuhl R (2008) A role for sex chromosome complement in the female bias in autoimmune disease. J Exp Med 205:1099–1108

Sneddon A (2019) Contributions of D1 vs. D2 receptor-expressing neurons in the nucleus accumbens core to compulsive-like alcohol consumption. Miami University Master Thesis

Sofuoglu M, Babb DA, and Hatsukami DK (2002) Effects of progesterone treatment on smoked cocaine response in women. Pharmacology, Biochemistry and Behavior 72:431-435.

Sofuoglu M, Dudish-Poulsen S, Nelson D, Pentel P. R., and Hatsukami D. K. (1999) Sex and menstrual cycle differences in the subjective effects from smoked cocaine in humans. Experimental and Clinical Psychopharmacology 7:274–283

Sofuoglu M, Dudish-Poulsen S, Nelson D, Pentel PR, and Hatsukami DK (1999) Sex and menstrual cycle differences in the subjective effects from smoked cocaine in humans. Experimental and Clinical Psychopharmacology 7:274-283.

Sofuoglu M, Mitchell E, and Kosten T (2004) Effects of progesterone treatment on cocaine responses in male and female cocaine users. Pharmacology Biochemistry and Behavior 78:699-705

Sofuoglu M, Mitchell E, and Kosten TR (2004) Effects of progesterone treatment on cocaine responses in male and female cocaine users. Pharmacology, Biochemistry and Behavior 78:699-705.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Song, Z., Yang, H., Peckham, E. M., & Becker, J. B. (2019). Estradiol-induced potentiation of dopamine release in dorsal striatum following amphetamine administration requires estradiol receptors and mGlu5. Eneuro, 6(1).

Stewart J, Woodside B, and Shaham Y (1996) Ovarian hormones do not affect the initiation and maintenance of intravenous self-administration of heroin in the female rat. Psychobiology 24:154-159.

Stoltman JJK, Woodcock EA, Lister JJ, Greenwald MK, and Lundahl LH (2015) Exploration of the telescoping effect among not-in-treatment, intensive heroin-using research volunteers. Drug Alcohol Depend 148:217-220.

Strong CE, Schoepfer KJ, Dossat AM, Saland SK, Wright KN, Kabbaj M (2017) Locomotor sensitization to intermittent ketamine administration is associated with nucleus accumbens plasticity in male and female rats. Neuropharmacology 121:195-203.

Sun W, Shchepkin D, Kalachev LV, Kavanaugh MP (2014) Glutamate transporter control of ambient glutamate levels. Neurochem Int 73:146-151.

Svikis DS, Miles DR, Haug NA, Perry B, Hoehn-Saric R, and McLeod D (2006) Premenstrual symptomatology, alcohol consumption, and family history of alcoholism in women with premenstrual syndrome. Journal of Studies on Alcohol 67:833-836.

Sylvestre MP, Chagnon M, Wellman RJ, Dugas EN, O'Loughlin J (2018) Sex differences in attaining cigarette smoking and nicotine dependence milestones among novice smokers. Am J Epidemiol 187:1670-1677.

Szumlinski KK, Shin CB (2018) Kinase interest you in treating incubated cocaine-craving? A hypothetical model for treatment intervention during protracted withdrawal from cocaine. Genes, Brain and Behavior 17:e12440.

Tang W, Wesley M, Freeman W, Liang B, and Hemby S (2004) Alterations in ionotropic glutamate receptor subunits during binge cocaine self-administration and withdrawal in rats. Journal of Neurochemistry 89:1021–1033

Tavares H, Martins SS, and Lob DSS (2003) Factors at play in faster progression for female pathological gamblers: an exploratory analysis. The Journal of Clinical Psychiatry 64:433-438.

Terner JM and de Wit H (2006) Menstrual cycle phase and responses to drugs of abuse in humans. Drug and Alcohol Dependence 84:1-13.

Thorner ED, Jaszyna-Gasior M, Epstein DH, Moolchan ET (2007) Progression to daily smoking: is there a gender difference among cessation treatment seekers? Substance Use & Misuse 42:829-235.

Torres OV, Natividad LA, Tejeda HA, Van Weelden SA, O'Dell LE (2009) Female rats display dose-dependent differences to the rewarding and aversive effects of nicotine in an age-, hormone-m and sex-dependent manner. Psychopharmacology (Berl) 206:303-312.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Towers E, Bakhi-Suroosh A, and Lynch W (2021) Females develop features of an addiction-like phenotype sooner during withdrawal than males. Psychopharmacology (Berl) 238:2213—2224

Towers E, Setaro B, and Lynch W (2022) Sex- and Dose-Dependent Differences in the Development of an Addiction-Like Phenotype Following Extended-Access Fentanyl Self-Administration. Frontiers in Pharmacology 13:841873

Towers E, Tunstall B, McCracken M, Vendruscolo L, and Koob G (2019) Male and female mice develop escalation of heroin intake and dependence following extended access. Neuropharmacology 151:189—194

Towers EB, Kilgore M, Abel, JM, Lynch WJ. Sex differences in the neuroadaptations underlying incubated cocaine-craving. Psychopharmacology, revised submission.

Townsend EA, Kim RK, Robinson HL, Marsh SA, Banks ML, Hamilton PJ (2021) Opioid withdrawal produces sex-specific effects on fentanyl-versus-food choice and mesolimbic transcription. Biological Psychiatry Global Open Science 1:112-122.

Trifilieff P and Martinez D (2014b) Imaging addiction: D2 receptors and dopamine signaling in the striatum as biomarkers for impulsivity. Neuropharmacology 76:498-509

Trifillieff P and Martinez D (2014a) Blunted dopamine release as a biomarker for vulnerability for substance use disorders. Biol Psychiatry 76:4-5

Urban N, Kegeles L, Slifstein M, Xu X, Martinez D, Sakr E, Castillo F, Moadel T, O'Malley S, Krystal J, and Abi-Darghama A (2010) Sex Differences in Striatal Dopamine Release in Young Adults After Oral Alcohol Challenge: A Positron Emission Tomography Imaging Study With [11C]Raclopride. Biological Psychiatry 68:689-696

Urbano-Marquez A, Estruch R, Fernandez-Sola J, Nicolas JM, Pare JC, Rubin E (1995) The greater risk of alcoholic cardiomyopathy and myopathy in women compared to men. JAMA 274:149-154.

van de Giessen, E., Weinstein, J. J., Cassidy, C. M., Haney, M., Dong, Z., Ghazzaoui, R., ... & Abi-Dargham, A. (2017). Deficits in striatal dopamine release in cannabis dependence. Molecular psychiatry, 22(1), 68-75

Vandergrift BJ, Hilderbrand ER, Satta R, Tai R, He D, You C, Chen H, Xu P, Coles C, Brodie MS, Lasek AW (2020) Estrogen receptor α regulates ethanol excitation of ventral tegmental area neurons and binge drinking in female mice. The Journal of Neuroscience 40:5196-5207.

Vandergrift BJ, You C, Satta R, Brodie MS, Lasek AW (2017) Estradiol increases the sensitivity of ventral tegmental area dopamine neurons to dopamine and ethanol. PLoS One doi:10.1371/journal.pone.01876956.

Vanderzeil A, Parker MA, Alshaarawy O (2020) Trends in heroin use among women of reproductive age in the United States, 2004-2017. Addictive Behaviors doi: 10.1016/j.addbeh.2020.106518.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Vassoler FM, Oranges ML, Toorie AM, and Byrnes EM (2018) Oxycodone self-administration during pregnancy disrupts the maternal-infant dyad and decreases midbrain OPRM1 expression during early postnatal development in rats. Pharmacology, Biochemistry and Behavior 173:74-83.

Verplaetse TL, Moore KE, Pittman BP, Roberts W, Oberleitner LM, Smith PH, Cosgrove KP, McKee SA (2018) Intersection of stress and gender in association with transitions in past year DSM-5 substance use disorder diagnoses in the United States. SAGE Journals doi:10.1177/2470547017752637.

Volkow N, Fowler J, Wang GJ, Swanson J, Telang F (2007) Dopamine in Drug Abuse and Addiction: Results of Imaging Studies and Treatment Implications. Arch Neurol. 64:1575-1579

Volkow ND, Chang L, Wang GJ, Fowler JS, Leonido-Yee M, Franceschi D, Sedler MJ, Gatley SJ, Hitzemann R, Ding YS, Logan J, Wong C, Miller EN (2001) Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. Am J Psychiatry doi:10.1176/appi.ajp.158.3.377.

Volkow ND, Ding YS, Fowler JS, Wang GJ (1996) Cocaine addiction: hypothesis derived from imaging studies with PET. Journal of Addictive Diseases 15:55-71.

Volkow ND, Fowler JS, Wang GJ, Hitzemann R, Logan J, Schlyer DJ, Dewey SL, Wolf AP (1993) Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. Synapse 14:169-177.

Volkow ND, Fowler JS, Wolf AP, Schlyer D, Shiue CY, Alpert R, Dewey SL, Logan J, Bendriem B, Christman D, Hitzemann R, Henn F (1990) Effects of chronic cocaine abuse on postsynaptic dopamine receptors. Am J Psychiatry 147:719-724.

Volkow ND, Han B, Compton WM, and McCance-Katz EF (2019) Self-reported medical and nonmedical cannabis use among pregnant women in the United States. JAMA 322:167-169.

Volkow ND, Tomasi D, Wang GJ, Logan J, Alexoff DL, Jayne M, Fowler JS, Wong C, Yin P, Du C (2014) Stimulant-induced dopamine increases are markedly blunted in active cocaine abusers. Molecular Psychiatry 19:1037-1043.

Volkow ND, Wang GJ, Fischman MW, Foltin RW, Fowler JS, Abumrad NN, Vitkun S, Logan J, Gatley SJ, Pappas N, Hitzemann R, Shea CE (1997) Relationship between subjective effects of cocaine and dopamine transporter occupancy. Nature 386:827-830.

Volkow ND, Wang GJ, Fowler JS, Logan J, Gatley SJ, Wong C, Hitzemann R, Pappas NR (1999) Reinforcing effects of psychostimulants in humans are associated with increases in brain dopamine and occupancy of D2 receptors. The Journal of Pharmacology 291:409-415.

Volkow ND, Wise RA, Baler R (2017) The dopamine motive system: implications for drug and food addiction. Nature Reviews Neuroscience 18:741-752.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Wagner FA, Anthony JC (2007) Male-female differences in the risk of progression from first use to dependence upon cannabis, cocaine, and alcohol. Drug and Alcohol Dependence 86:191-198.

Wand GS, Oswald LM, McCaul ME, Wong DF, Johnson E, Zhou Y, Kuwabara H, Kumar A (2007) Association of amphetamine-induced striatal dopamine release and cortisol responses to psychological stress. Neuropsychopharmacology 32:2310–2320

Wang C, Zheng D, Xu J, Lam W, and Yew D (2013) Brain damages in ketamine addicts as revealed by magnetic resonance imaging. Front. Neuroanat.

Wang M and Arnsten AFT (2015) Contribution of NMDA receptors to dorsolateral prefrontal cortical networks in primates. Neurosci Bull 31:191-197.

Warren JG, Fallon VM, Goodwin L, Gage SH, and Rose AK (2021) Menstrual cycle phase, hormonal contraception, and alcohol consumption in premenopausal females: a systematic review. Front Glob Womens Health 2:745263.

Weinland C, Muhle C, Kornhuber J, and Lenz B (2021) Progesterone serum levels correlate negatively with craving in female postmenopausal in-patients with alcohol use disorder: a sex- and menopausal status-separated study. Progress in Neuropsychopharmacology and Biological Psychiatry 110:110278.

White KA, Brady KT, and Sonne S (1996) Gender differences in patterns of cocaine use. The American Journal on Addictions 5:259-261.

White TL, Justice AJH, and de Wit H (2002) Differential subjective effects of d-amphetamine by gender, hormone levels and menstrual cycle phase. Pharmacology, Biochemistry and Behavior 73:729-741.

Wiers C, Shokri-Kojori E, Cabrera E, Cunningham S, Wong C, Tomasi D, Wang GJ, and Volkow N (2016) Socioeconomic status is associated with striatal dopamine D2/D3 receptors in healthy volunteers but not in cocaine abusers. Neuroscience Letters 617:27-31

Wiers CE, Cabrera EA, Tomasi D, Wong CT, Demiral SB, Kim SW, Wang GJ, Volkow ND (2017) Striatal dopamine D2/D3 receptor availability varies across smoking status. Neuropsychopharmacology 42:2325-2332.

Wiers CE, Shokri-Kojori E, Wong CT, Abi-Dargham A, Demiral SB, Wang GJ, Volkow ND (2016) Cannabis abusers show hypofrontality and blunted brain responses to a stimulant challenge in females but not in males. Neuropsychopharmacology 41:2596-2605.

Wissman AM, McCollum AF, Huang GZ, Nikrodhanond AA, Woolley CS (2011) Sex differences and effects of cocaine on excitatory synapses in the nucleus accumbens. Neuropharmacology 61:217–227

Wolf ME, Tseng KY. Calcium-permeable AMPA receptors in the VTA and nucleus accumbens after cocaine exposure: when, how, and why? Front Mol Neurosci. 2012;5:72.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Woodcock E, Zakiniaeiz Y, Morris E, and Cosgrove K (2020) Sex and the dopaminergic system: Insights from addiction studies. Handbook of Clinical Neurology 175:141-165

Worhunsky PD, Matuskey D, Gallezot JD, Gaiser EC, Nabulsi N, Angarita GA, Calhoun VD, Malison RT, Potenza MN, Carson RE (2017) Regional and source-based patterns of [11 C]-(+)-PHNO binding potential reveal concurrent alterations in dopamine D2 and D3 receptor availability in cocaine-use disorder. Neuroimage 148:343-351.

Yoest KE, Quigley JA, Becker JB (2018) Rapid effects of ovarian hormones in dorsal striatum and nucleus accumbens. Horm Behav 104:119-129.

Younis JS, Iskander R, Fauser BCJ, Izhaki I (2020) Does an association exist between menstrual cycle length within the normal range and ovarian reserve biomarkers during the reproductive years? A systematic review and meta-analysis. Hum Reprod Update 26:904-928.

Zahr NM, Mayer D, Rohlfing T, Chanraud S, Gu M, Sullivan EV, Pfefferbaum A (2013) In vivo glutamate measured with MR Spectroscopy: behavioral correlates in aging. Neurobiol Aging 34:1265-1276.

Zakiniaeiz Y, Hillmer AT, Matuskey D, Nabulsi N, Ropchan J, Mazure CM, Picciotto MR, Huang Y, McKee SA, Morris ED, Cosgrove KP (2019) Sex differences in amphetamine-induced dopamine release in the dorsolateral prefrontal cortex of tobacco smokers. Neuropsychopharmacology 44:2205-2211.

Zhang D, Yang S, Yang C, Jin G, Zhen X (2008) Estrogen regulates responses of dopamine neurons in the ventral tegmental area to cocaine. Psychopharmacology 199:625-635.

Zhao W and Becker JB (2010) Sensitization enhances acquisition of cocaine self-administration in female rats: estradiol further enhances cocaine intake after acquisition. Hormones and Behavior 58:8-12.

Zimmer B, Oleson E, and Roberts D (2012) The Motivation to Self-Administer is Increased After a History of Spiking Brain Levels of Cocaine. Neuropsychopharmacology 37:1901—1910

Zuloaga, D. G., Johnson, L. A., Agam, M., & Raber, J. (2014). Sex differences in activation of the hypothalamic–pituitary–adrenal axis by methamphetamine. Journal of neurochemistry, 129(3), 495-508.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Footnotes

Acknowledgements

The authors would like to thank Katriel E. Cho for creating the graphical abstract.

Funding

This work was supported by NIDA grants R01DA024716, R01DA052893, and R21DA049992 (Lynch) and R01DA048638 (Lynch and Rissman), a Pharmacological Sciences Training Grant 5T32GM007055-47 (Towers), and a MSTP Training Grant T32 GM007267 (Towers).

Conflict-of-Interest Statement

No author has an actual or perceived conflict of interest with the contents of this article

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Figure Legend

Figure 1. Biological basis for the faster course from drug use to addiction/SUD in females. Females are more sensitive to the positive reinforcing effects of drugs and acquire drug self-administration faster than males. This is mediated through interactions of estradiol and mGlu5, both of which increase drug-evoked dopamine signaling in the mesolimbic reward pathway of females. Craving and motivation to use addictive drugs is typically low during early abstinence, particularly in females, but both features become progressively enhanced over a period of protracted abstinence. Molecular adaptations in response to chronic drug use and abstinence differ between males and females and may drive sex differences in anhedonia, craving, and relapse vulnerability during both early and late abstinence. Addiction-like features, including an enhanced motivation for the drug, compulsive drug use, and vulnerability to relapse, emerge sooner during abstinence and/or after less drug intake in females than males indicating that the telescoping effect is biological based. This effect is likely driven by interactions of estradiol and mGlu5 which cause an earlier recruitment of the glutamate system (i.e. AMPA receptors). Once addiction has developed, behavioral differences between males and females become subtle and often depend on estrous cycle phase (e.g., drug craving). The neuroadaptations that underlie addiction also differ between males and females (e.g., NMDA receptor signaling in the dorsomedial prefrontal cortex), even in the absence of behavioral differences. E2=estradiol. DA=Dopamine. AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor.

Figure 2. Rat model of the telescoping effect with cocaine. Data are plotted as mean percent change (±SEM) from the average number of infusions obtained during three baseline progressive-ratio sessions prior to extended-access cocaine self-administration (24-hr/day, 4 discrete trials/hr, 1.5 mg/kg/infusion, 7-10 days; refs) versus those obtained at retest following extended-access cocaine self-administration and 0, 7, 10, 14, or 60 days of abstinence. Motivation for cocaine increased progressively over abstinence following extended-access cocaine self-administration. Neither males or females showed an increase in motivation for cocaine when responding was assessed immediately following extended-access self-administration (0 days abstinent; Lynch and Taylor 2005); in fact, motivation was significantly decreased from baseline in females in the 0-day group. Females, but not males, showed an increase in motivation for cocaine when responding was assessed following 7 (Towers et al. 2021) or 10 days of abstinence (Lynch and Taylor 2004). Both males and females showed an increase in motivation for cocaine when responding was assessed following 14 days of abstinence (Towers et al. 2021) and motivation was highest in both males and females when responding was assessed following 60 days of abstinence (Towers et al. 2021). The threshold for the development of an addiction-like phenotype, as defined by ≥15% increase from baseline and as represented by a dotted line, developed sooner during abstinence in females than males (following 7 versus 14 days of abstinence). Significant difference from baseline/no change (*). Data were redrawn, with permission, from the above cited references.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Table 1. Glossary of the key terms used in this review.

Term	Definition
Addition-like feature	The expression of a behavior in an animal that resembles a criterion, or symptom, of SUD in humans as defined by the DSM-5 (American Psychiatric Association, 2013). Some of the more commonly modeled features include escalation of drug intake over time, binge/abstinent patterns of drug intake, physical dependence, an enhanced motivation to obtain the drug, compulsive drug use despite adverse consequences, preference for the drug over a non-drug rewards, and enhanced drug-craving/vulnerability to relapse (Lynch 2018).
Addition-like phenotype	The expression in an animal of one or more characteristics (or addiction-like features) that resemble features of SUD in humans as defined by the DSM-5. For example, the development of an enhanced motivation for the drug has been used to define the development of an addiction-like phenotype since, as in humans, once this feature emerges, it appears to represent a relatively permanent shift to a higher motivational state (Lynch 2018).
Acquisition procedure	A procedure that uses a set of performance criteria to define the time-point when an animal has learned a new behavior, such as lever pressing to obtain infusions of a drug. Acquisition procedures can be a strong tool for investigating individual differences in sensitivity to the reinforcing effects of a drug. These effects are ideally studied under low dose conditions and the question asked is "which animals can detect the reinforcing effects of this low dose of the drug". A faster speed of acquisition and/or greater percent group acquisition is then used to define an enhanced vulnerability to substance use (Lynch et al. 2010).
Animal model of substance use	A model used to assess initial vulnerability to use addictive drugs. Short-access drug self-administration procedures (1-2 hr/day access) are commonly used and focus on rates and/or percent group acquisition of drug self-administration, maintenance levels of drug use, or motivation to obtain the drug, as assessed using a progressive-ratio schedule or a within-session threshold procedure, following acquisition.
Animal model of substance use disorder	A model that has been validated to induce an addiction-like phenotype in animals like that observed in humans with SUD. Extended-access drug self-administration procedures (≥ 6 hr/day access) are the gold-standard for inducing addiction-like features in animals (Lynch 2018).
Binge/abstinent pattern	A binge-abstinent of pattern of drug self-administration is characterized by cycles of heavy/prolonged periods of drug use (binge intake) separated by periods of self-imposed abstinence.
Choice procedure	A procedure used to determine percent choice, or preference, for one reinforcer over another (or for different magnitudes of a reinforcer). Choice procedures can be a powerful approach for determining individual differences in vulnerability to developing a preference for the drug over other non-drug rewards, such as a highly palatable food reward, and for determining potential interventions that reverse a drug preference back to a non-drug one.
Compulsive drug use	A core feature of addiction in humans that is modelled in animals using punishment or choice procedures. The development of this addiction-like feature has been defined as continued drug use despite adverse consequences (e.g. coincident shock) or an exclusive choice (>90%) of the drug over an alternative non-drug reward (Lynch 2018). This addiction-like feature emerges following abstinence l (7 days or more) from extended-access self-administration and the magnitude of its expression increases with longer periods of abstinence (Towers et al. 2021).
Enhanced motivation to obtain	A core feature of addiction in humans that is modelled in animals using either a progressive ratio schedule or the

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

the drug	threshold procedure. This feature has been defined as ≥15% increase in motivation for the drug relative to short-access controls or baseline prior to extended-access self-administration and abstinence (Lynch 2018). This addiction-like feature emerges following abstinence (7 days or more) from extended-access self-administration and the magnitude of its expression increases with longer periods of abstinence (Towers et al. 2021).
Enhanced drug-craving/vulnerability to relapse	A core feature of addiction in humans that is modelled in animals using an extinction/reinstatement procedure or a cue-induced drug-seeking procedure. This addiction-like feature is typically assessed following extended-access self-administration and a period of protracted abstinence (>14 days) since these conditions induce high levels of drug-seeking relative to short-access controls and earlier abstinence time-points. The expression of this addiction-like feature progressively increases, or incubates, over abstinence (Lynch 2018).
Escalation of drug intake	Escalation of drug intake occurs in animals given extended-access, but not short-access, to the drug and is characterized by a gradual increase in drug intake over time. It is ideally studied following acquisition of drug self-administration, to ensure that increases in intake are reflective of escalation rather than acquisition, and is thought to resemble the loss of control over drug intake feature observed in humans with SUD (Koob 2021).
Fixed-ratio schedule	A schedule of reinforcement in which a set number of responses (e.g., 1, 2, or 10) produce a reinforcer delivery, such as a drug infusion.
Gender	The characterization of women or men that is socially constructed and varies over time and between cultures (Committee on Understanding the Biology of Sex and Gender Differences 2001).
Incubation effect	The incubation effect refers to a progressive increase in drug-seeking from early to later periods of abstinence following extended-access self-administration. A similar phenomenon has also been reported in humans with SUD (Li et al. 2015) and is thought to reflect the development of an enhanced vulnerability to relapse. A similar incubation effect has also been observed for the development of other addiction-like features, including compulsive drug use and an enhanced motivation to obtain the drug (Towers et al. 2021; Gancarz-Kausch et al. 2014).
Intermittent-access procedure	A drug self-administration procedure wherein access to the drug is intermittently available, such as in 5-min trials with unrestricted, fixed-ratio 1 access, or in discrete trials, With the most commonly used procedures, animals either have unrestricted, fixed-ratio 1 access to the drug infusions in 5 min trials that initiate every 30 minutes for 6 or more hours/day or to single infusions of the drug in discrete trials that initiate every 15 min 12-24-hr/day (Fitch and Roberts 1993; Zimmer et al. 2012). Intermittent-access self-administration results in a binge-abstinent pattern of drug intake and spiking brain drug levels (Zimmer et al. 2012).
Long-access procedure	A drug self-administration procedure that allows continuous, fixed-ratio 1 access to the drug for ≥6 hr/day. This results in high levels of drug intake and an escalating pattern of drug use (Ahmed and Koob 1998).
Physical dependence	A core feature of addiction in humans that is assessed in animal models following chronic drug self-administration and defined by withdrawal-induced weight loss and somatic signs of withdrawal (e.g., abdominal constriction, salivation, ptosis, paw tremors; Lynch et al. 2010).
Preference for the drug over a non-drug reward	A core feature of addiction in humans that is modelled in animals using a choice procedure. The development of this addiction-like feature is defined as an exclusive choice (>90%) for the drug versus a non-drug reward (Lynch 2018).
Progressive-ratio schedule	A schedule of reinforcement that requires the animal to emit an increasing amount of work (or lever pressing) to

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

	obtain each subsequent delivery of the drug within a session. The breakpoint, or the point that the animal stops responding, is used as a measure of motivation to obtain the drug.
Punishment procedure	Punishment procedures decrease the probability of responding for the reinforcer. For example, when an aversive stimulus, such as electric shock, is paired with the delivery of the drug, drug-taking decreases. Punishment procedures have also been used to demonstrate compulsive use, a core feature of addiction in humans, wherein animals show a reduced sensitivity to punishment and continue to self-administer high levels of the drug.
Reinstatement procedure	A model of relapse/drug-craving whereby the animal is tested on responding on a lever that was formerly associated with the drug under non-reinforced conditions (extinction), and once responding has reached a certain level of non-responsiveness, the reinstatement of drug-seeking (responding on this same lever) is examined in response to presentations of drug-associated cues, a small "priming" dose of drug, or stress.
Sex	The characterization of an individual as female or male according to their reproductive organs and functions derived from their chromosomal complement (generally XX for female and XY for male; Committee on Understanding the Biology of Sex and Gender Differences, 2001).
Short-access procedure	A drug self-administration procedure wherein animals have access to the drug for 1-2 hr/day. Such access results in relatively stable and low levels of drug intake from day-to-day.
Telescoping effect	A phenomenon that describes a faster progression in females compared to males from initial drug use to meeting the criteria and/or seeking treatment for a SUD (Piazza et al. 1989).
Threshold procedure	A procedure used to examine motivation to obtain a reinforcer. For example, the demand for a drug is measured by varying the price (response requirement) and the value (dose) of the drug within a session (Zimmer et al. 2012).

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Table 2a. Summary of human studies on the telescoping effect within treatment-seeking individuals.

Source	Drug	Subjects	Telescoping Findings: Time (in years unless stated otherwise) Between Events
Diehl et al. (2007)	Alcohol	106W/106M	**W<M:** regular use to dependence (10.0 vs 11.6) **W<M:** dependence to treatment (4.5 vs 7.9)
Johnson et al. (2005)	Alcohol	785W/1252M	**W<M:** regular use to problematic use in the older (30+; 7.6 vs 10.9), but not younger age group (<29; 4.9 vs 5.2)
Randall et al. (1999)	Alcohol	419W/1307M	**W<M:** regular use to problematic use (0.9 vs 2.3) **W<M:** loss of control over use to severe alcohol-related problems (5.5 vs 7.8) **W<M:** regular use to seeking treatment (11.6 versus 15.8)
Lewis and Nixon (2014)	Alcohol	257W/274M	**W<M:** milestones (first use, first intoxication, regular use, problematic use) to treatment (18.1 vs 23.0, 15.5 vs 20.7, 13.0 vs 18.2, 10.3 vs 14.5) **W=M:** milestones (first use, first intoxication, regular use) to problematic use/dependence (8.9 vs 9.7, 6.3 vs 7.4, 3.2 vs 4.5)
Ashley et al. (1977)	Alcohol	135W/736M	**W<M:** problematic use to treatment (14.1 vs 20.2)
Hesselbrock et al. (1985)	Alcohol	90W/231M	**W<M:** initial use to problematic use/dependence (7.4 vs 15.0)
Piazza et al. (1989)	Alcohol	33W/105M	**W<M:** problematic use to treatment (10.4 vs 14.7) **W=M:** initial use to first intoxication (2.9 vs 1.7) **W=M:** first intoxication to problematic use (14.0 vs 14.7)
Mann et al. (1992)	Alcohol	14W/51M	**W<M:** initial use to treatment (3.8 vs 9.2)
Mann et al. (2005)	Alcohol	42W/34M	**W<M:** problematic use/dependence to treatment (5.6 vs 10.4)
McCance-Katz et al. (1999)	Alcohol, Cocaine	92W/206M	**W<M:** initial alcohol use to treatment (8.8 vs 11.4) **W<M:** initial cocaine use to treatment (5.2 vs 5.8)
Hernandez-Avila et al. (2004)	Alcohol, Cannabis, Opioids	156W/115M	**W<M:** regular alcohol use to treatment (14.5 vs 19.0) **W<M:** regular cannabis use to treatment (13.0 vs 18.0) **W<M:** regular opioid use to treatment (8.0 vs 12.0)
Griffin et al. (1989)	Cocaine	34W/95M	**W<M:** initial use to treatment (9.0 vs 10.2)
White et al. (1996)	Cocaine	27W/60M	**W<M:** initial use to problematic use (1.6 vs 3.3) **W<M:** initial use to treatment (5.1 vs 10.4)
Haas and Peters (2000)*	Alcohol, Cocaine, Cannabis	42W/118M	**W< M:** initial cocaine use to problematic use (4.3 vs 9.8) **W=M:** initial alcohol or cannabis use to problematic use (2.2 vs 1.9)
Lewis et al. (2014)	Cocaine, Cannabis, Opioids	288W/255M	**W=M:** regular cocaine use to problematic use (1.1 vs 1.8) **W<M:** regular opioid use to problematic use (0.5 vs 2.7) **W<M:** regular cannabis use to problematic use (0.7 vs 2.0[#])
Tavares et al. (2003)	Gambling	70W/70M	**W<M:** milestones (social, intense, and problematic gambling) to treatment (5.0 vs 7.9, 0.8

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

			vs 4.3, 1.9 vs 6.7)
Ladd and Petry (2002)	Gambling	45W/70M	**W<M:** problematic gambling to treatment (4.4 vs 14.6)
Ibanez et al. (2003)	Gambling	22W/47M	**W<M:** initial gambling to problematic gambling (4.2 vs 11.0)
Grant et al. (2012)	Gambling	34W/37M	**W<M:** initial gambling to problematic gambling (8.3 vs 12.0)
Brecht et al. (2004)	METH	154W/196M	**W<M:** initial use to regular use (1.6 and 2.6 years[#])
Peltier et al. (2021)	Opioids	2794W/45614M	**W<M:** age diagnosed with OUD (44.9 vs 51.0)
Anglin et al. (1987)	Opioids	264W/282M	**W<M:** months from initial use to daily use (14 vs 21)
Adelson et al. (2018)	Opioids	494W/762M	**W<M:** initial heroin use to treatment (12.9 vs 14.8)
Hser et al. (1987)	Opioids	264W/282M	**W<M:** months from daily use to treatment (82.5 vs 98.0)

*this treatment population underwent forced treatment due to a drug court program. [#]trend for significant difference (P<0.1). M=men. W=women. n.s.= non-significant, METH, methamphetamine

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Table 2b. Summary of human studies on the telescoping effect within nontreatment-seeking individuals.

Source	Drug	Subjects	Telescoping Findings: Time (in years unless stated otherwise) between events
Alvanzo et al. (2011)	Alcohol	11862W/9244M	**W=M:** initial use to dependence (4.9 vs 5.4)
Keyes et al. (2010)	Alcohol	30125W/23113M	**W=M:** initial use to dependence in overall sample (5.6 and 5.8) **W<M:** initial use to dependence in cohort 2 only (3.7 vs 4.2) **W<M:** dependence to treatment in overall sample (6.1 vs 7.0) and in one of 5 cohorts (cohort 5, 19.4 vs 23.5)
Huggett et al. (2018)	Alcohol, Tobacco	1477W/1297M	**W≤M:** initial alcohol use to dependence (3.3 vs 3.8[#]) **W=M:** initial tobacco use to dependence (4.5 vs 4.5)
Khan et al. (2013)	Cannabis	1217W/2080M	**W<M:** initial use to dependence (2.2 vs 2.6)
Ehlers et al. (2010)	Cannabis	177W/172M	**W<M:** initial use to dependence (44.7 vs 49.3)
Sofuoglu et al. (1999)	Cocaine	21W/23M Study 1 12W/11M Study 2	**W<M:** initial use to dependence in two human laboratory studies (Study 1, 9.2 vs 11.3; Study 2, 7.4 vs 13.0)
O'Brien and Anthony (2005)	Cocaine	59488W/54753M	**W<M:** initial use to dependence (defined by risk within 24 months of first use, W 3-4 times more likely than M)
Slutske et al. (2015)	Gambling	2662W/2001M	**W>M:** initial gambling to weekly/problematic gambling, disordered gambling symptoms, and diagnosis of disordered gambling (8.6 vs 8.1, 10.9 vs 8.3, 12.9 vs 10.9)
DiFranza et al. (2002)	Tobacco	679W/M[+]	**W<M:** days from monthly smoking to dependence symptoms (21 days vs 183 days)
Scragg et al. (2008)	Tobacco	14925W/10070M[+]	**W<M:** initial use to dependence (W had less use than M prior to symptoms onset)
DiFranza et al. (2007)	Tobacco	647W/599M[+]	**W=M:** days from initial use to nicotine/tobacco dependence, symptoms, and autonomy loss (no sex effect, data not stated)
Sylvestre et al. (2018)	Tobacco	471W/368M[+]	**W<M:** initial use to dependence symptoms (21 days vs 183 days)
Thorner et al. (2007)	Tobacco	378W/261M[+]	**W<M:** initial use to daily use (0.9 vs 1.3)
Stoltman et al. (2015)	Opioids	165W/389M	**W=M:** initial heroin use to problematic use (2.1 vs 2.5)
Back et al. (2011)	Opioids	12W/12M	**W<M:** initial use to regular use (5.0 vs 8.1)

[+]Conducted in children/adolescents. [#]trend for significant difference (P<0.1). M=men. W=women. n.s., non-significant.

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Table. 3 Summary of preclinical studies on the telescoping effect.

Source	Drug (dose/inf)	Rats	SA conditions	Addiction feature measured (procedure)	Vulnerability to developing addiction-like features
Kerstetter et al. 2012	Cocaine (0.4, 1.0 mg/kg)	39M/29F	**ShA** (FR1, up to 20 inf or food pellets, 5 days each)	**Preference for drug over other rewards (choice procedure):** Cocaine (0.4 or 1.0 mg/kg) vs food (45 mg pellet). Sessions began after acquisition and were run for 5 days.	**F>M**. Females were more likely than males to choose cocaine (low and high dose) over food (low dose, 59% vs 33%; high dose, 76% vs 68%)
Perry et al. 2013	Cocaine (0.4 mg/kg)	12M/12F	**ShA** (30-min each: pellet only, cocaine only, cocaine vs pellet choice; FR1, 1st 3 days then FR5 for 21 days)	**Preference for drug over other rewards (choice procedure):** Cocaine vs banana-flavored food pellet (45 mg pellet). Choice testing occurred daily after the pellet and cocaine only sessions.	**F>M.** Females were likelihood than males to develop a preference for cocaine over food (50% vs 17%)
Perry et al. 2015	Cocaine (0.4 mg/kg)	50M/50F	**ShA** (30-min each: pellet only, cocaine only, cocaine vs pellet choice; FR1, 1st 3 days then FR5 for 21 days)	**Preference for drug over other rewards (choice procedure):** Cocaine vs banana-flavored food pellet (45 mg pellet). Choice testing occurred daily after the pellet and cocaine only sessions.	**F>M**. Females were more likely than males to develop a preference for cocaine over food (42% vs 26%)
Kawa and Robinson, 2019	Cocaine (0.4 mg/kg)	28M/24F	**ShA** (intermittent-access: 2, 5-min trials/hr, 5-hr/day, 5 days/wk, 30 days)	**Enhanced motivation for the drug (threshold procedure):** Threshold tests (FR1, progressively decreasing doses of cocaine 1.28 to 0.004 mg/kg) were run following the tenth and 30th day of SA and again after 14 days of abstinence.	**F>M**: Females developed an enhanced motivation for cocaine after less abstinence than males (i.e. following ten days of SA vs following 30 days of SA and 14 days of abstinence)
Lynch and Taylor, 2004	Cocaine (1.5 mg/kg)	18M/20F	**ExA** (4, 10-min trials/hr, 24- hr/day, 7 days)	**Enhanced motivation for the drug (PR schedule):** PR testing with cocaine (0.5 mg/kg) was conducted prior to ExA SA and then again after ExA SA and 7 days of abstinence (3 sessions each)	**F>M**: Females, but not males, developed an enhanced motivation for cocaine under these threshold conditions.
Towers et al. 2021	Cocaine (1.5 mg/kg)	39M/38F	**ExA** (4, 10-min trials/hr, 24-hr/day, 10 days)	**Enhanced motivation for the drug (PR schedule):** PR testing with cocaine (0.5 mg/kg) was conducted prior to ExA SA and then again after ExA SA and 7, 14, or 60 days of abstinence (3 sessions each). **Compulsive use (histamine-punishment):** Following the third PR session, histamine (0.4 mg/kg) was added to the cocaine solutions and three additional PR sessions were run.	**F>M**: Females develop an enhanced motivation for cocaine sooner during abstinence than males (7 vs 14 days) **F>M**: Females tested following 7 days of abstinence displayed greater compulsive use than males; males required more abstinence to reach the-female level of compulsivity (14 days).
Townsend et al. 2021	Fentanyl (0.32, 1.0 3.2, 10.0 ug/kg)	18M/17F	**ExA** (FR5, 12-hr/day, 5-day/wk, 3 weeks)	**Preference for drug over other rewards (choice procedure).** Fentanyl vs Ensure. Tested at the end of each week of ExA SA 8hr after last ExA session	**F<M**: Males, but not females, showed withdrawal-induced increases in preference for fentanyl (at low doses), and methadone attenuated this effect.

M, male; F, female; FR, fixed-ratio; PR, progressive-ratio; ShA, short-access; ExA, extended-access, SA, self-administration.

Pharmrev Fast Forward. Published on 12 December 2022 as DOI 10.1124/pharmrev.121.000361 This article has not been copyedited and formatted. The final version may differ from this version.

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

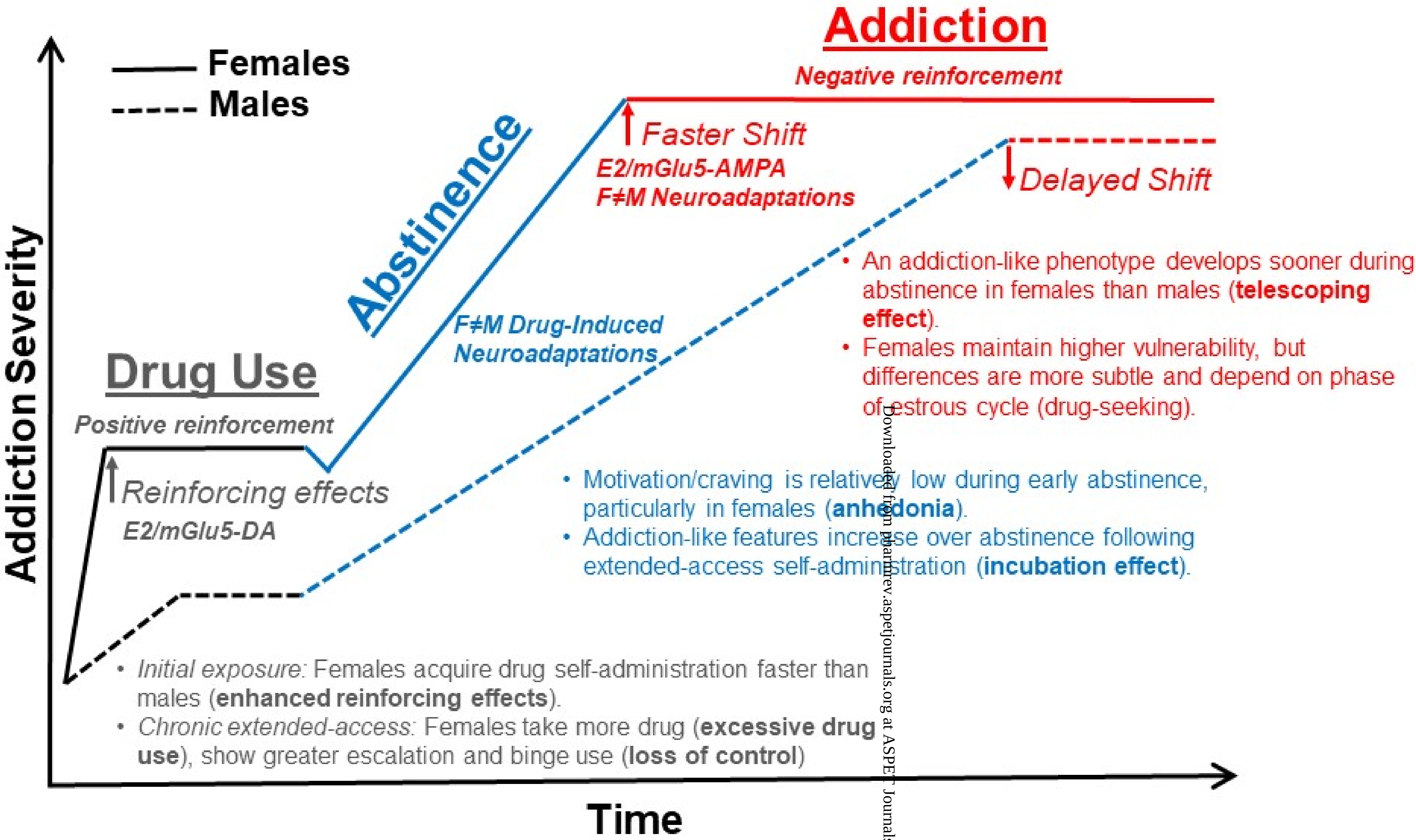
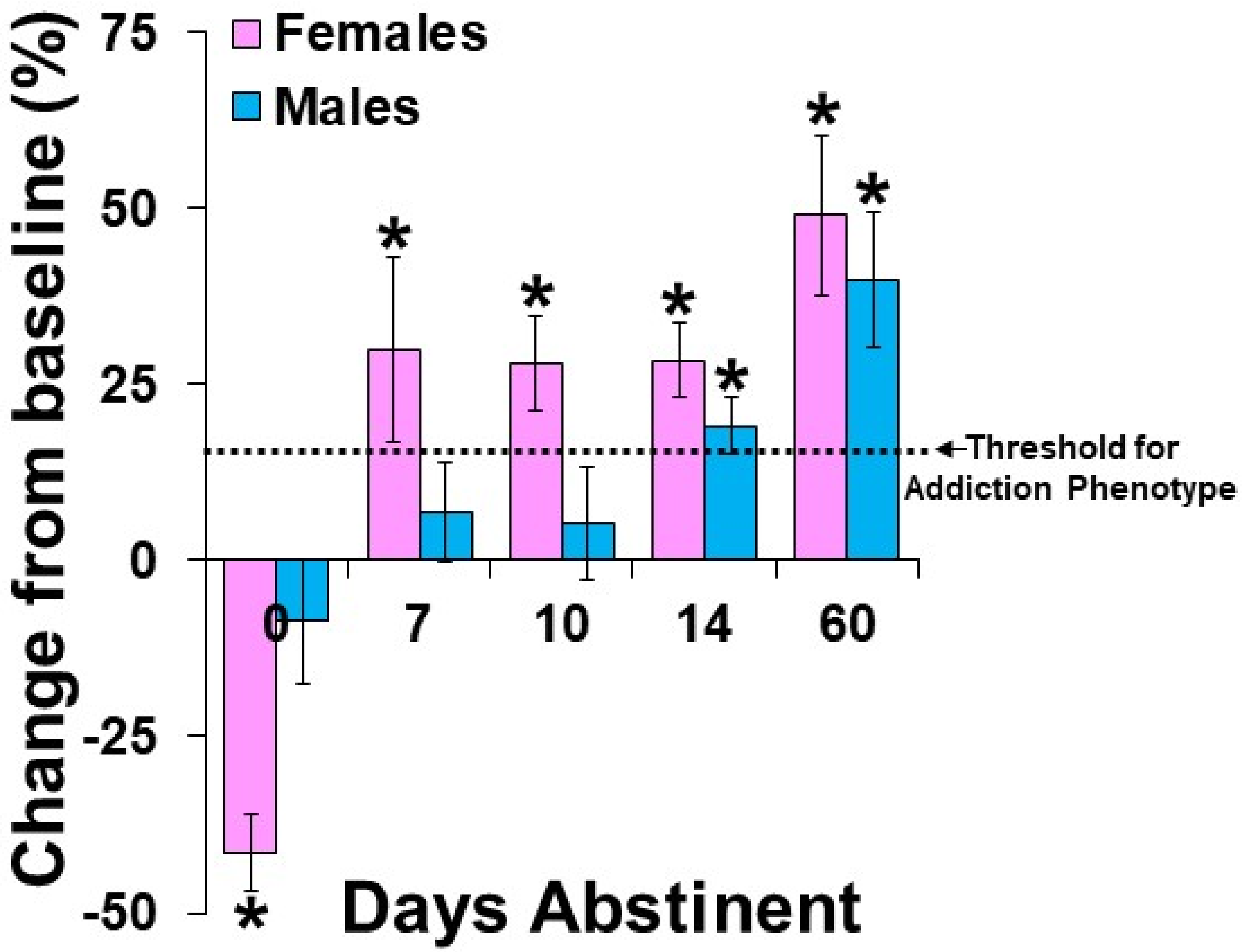


Fig. 1

Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024



Downloaded from pharmrev.aspetjournals.org at ASPET Journals on April 20, 2024

Fig. 2