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Review

Modeling the development of drug addiction in male and female animals

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ABSTRACT

An increasing emphasis has been placed on the development and use of animal models of addiction that capture defining features of human drug addiction, including escalation/binge drug use, enhanced motivation for the drug, preference for the drug over other reward options, use despite negative consequences, and enhanced drug-seeking/relapse vulnerability. The need to examine behavior in both males and females has also become apparent given evidence demonstrating that the addiction process occurs differently in males and females. This review discusses the procedures that are used to model features of addiction in animals, as well as factors that influence their development. Individual differences are also discussed, with a particular focus on sex differences. While no one procedure consistently produces all characteristics, different models have been developed to focus on certain characteristics. A history of escalating/binge patterns of use appears to be critical for producing other features characteristic of addiction, including an enhanced motivation for the drug, enhanced drug seeking, and use despite negative consequences. These characteristics tend to emerge over abstinence, and appear to increase rather than decrease in magnitude over time. In females, these characteristics develop sooner during abstinence and/or following less drug exposure as compared to males, and for psychostimulant addiction, may require estradiol. Although preference for the drug over other reward options has been demonstrated in non-human primates, it has been more difficult to establish in rats. Future research is needed to define the parameters that optimally induce each of these features of addiction in the majority of animals. Such models are essential for advancing our understanding of human drug addiction and its treatment in men and women.

1. Introduction

The vast majority of the preclinical data on drug addiction are based on studies conducted in male animals self-administering drugs under short access self-administration conditions (e.g., 1–2 h/day, fixed ratio 1 schedule). Drug intake under these conditions is stable from day-to-day, and intake is relatively low (Lynch and Carroll, 2001). These studies have been incredibly useful for determining the neurobiological basis for drug reinforcement and have helped identify a number a factors that predict a vulnerability to initial drug use (Campbell and Carroll, 2000; Deminiere et al., 1989; Wise and Bozarth, 1981; Wise and Koob, 2014). Short access conditions, however, by virtue of their stability, may not capture critical features of addiction in humans, and as such, the behavioral and neurobiological principles defined by these studies may be restricted to drug reinforcement and initial vulnerability, but not characteristic of "addiction". Specifically, while the reinforcing effects of drugs are critically involved addiction, particularly during early stages, these effects may diminish over time as the disease progresses (Koob and Volkow, 2016). Other factors also appear to be critical to maintaining drug use, particularly once addiction has developed, such as loss of control over drug use and the resulting excessive use of the drug, and the negative reinforcing effects of drugs (i.e., use to alleviate withdrawal or craving; Koob and Mason, 2016).

In humans, addiction, or substance use disorders, has been defined in the DSM-5 as meeting two or more of 11 diagnostic criteria (American Psychiatric Association, 2013). These criteria focus on evidence of impaired control over drug use, such as an increased time and energy spent seeking and using the drug, intense craving and urge to use the drug, and an inability to reduce or abstain from drug use, and social impairment and compulsive drug use, such as drug use to the exclusion of other activities and despite negative consequences. While no one animal model captures all of the behavioral, pharmacological, and social aspects of addiction, numerous procedures have been developed to focus on one of more of the critical features. Five of the more commonly modeled features of addiction include: 1) escalation/binge patterns of drug use, 2) enhanced motivation for the drug, 3) preference for the drug over other reward options, 4) use despite negative consequences, and 5) enhanced drug-seeking/relapse vulnerability. A greater emphasis is being placed on capturing these features of addiction in animal models given accumulating evidence showing that the neurobiological mechanisms underlying drug taking and seeking behavior change with the development of addiction-like behaviors (for

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review see Koob, 2014; Wolf, 2016; Wolf and Tseng, 2012; also see Ben-Shahar et al., 2007; Briand et al., 2008; Cohen et al., 2015; Conrad et al., 2008; Doyle et al., 2014; Fischer et al., 2013; Fischer-Smith et al., 2012; George et al., 2008; Greenwell et al., 2009; Hao et al., 2010; Imperio and Grigson, 2015; Le Cozannet et al., 2013; Mateo et al., 2005; Ramôa et al., 2014; Recinto et al., 2012; Zorrilla et al., 2012).

There is also an increased emphasis placed on the inclusion of females in studies of addiction particularly in light of mounting evidence from humans and animals demonstrating that the addiction process occurs differently in males and females (Becker and Koob, 2016; Bobzean et al., 2014; Carroll et al., 2004; Carroll and Lynch, 2016; Fattore et al., 2008; Lynch et al., 2010). In humans, although men are more likely than women to use drugs and have addictive disorders, women are more vulnerable than men on certain aspects of drug addiction (Elton and Kilts, 2010; Greenfield et al., 2010; Zilberman et al., 2003). One of the most striking examples is “the telescoping effect” where following initial drug use, women meet criteria for substance abuse disorders and seek treatment after fewer years of drug use as compared to men (Anglin et al., 1987; Brady and Randall, 1999; Griffin et al., 1989; Haas and Peters, 2000; Hernandez-Avila et al., 2004; McCance-Katz et al., 1999; Westermeyer and Boedicker, 2000). Women also report longer periods of use following abstinence (Gallop et al., 2007), and are more likely than men to attribute relapse to drug use to reasons of depression and negative affect (McKay et al., 1996). Similar findings have also been reported in preclinical studies with results showing that female animals self-administer more drug under extended access conditions, and develop certain characteristics of addiction faster and/or following less drug exposure than male animals (Anker and Carroll, 2011; Becker and Koob, 2016; Lynch, 2006; Lynch and Taylor, 2004). Cumulative evidence from both humans and animals suggest that the ovarian hormones estradiol and progesterone modulate vulnerability in females (Anker and Carroll, 2011; Flores et al., 2016; Ford et al., 2002, 2004; Kucerova et al., 2009; Larson et al., 2007; Lynch et al., 2001; Lynch and Taylor, 2005; Lynch and Sofouglu, 2010; Wetherill et al., 2016), with results from animals further suggesting for that estradiol may be necessary for the development of features of psychostimulant addiction (Kerstetter et al., 2012; Ramôa et al., 2013, 2014). These preclinical and clinical data show good correspondence indicating that sex differences in drug addiction are biologically based. These findings also suggest that sex and hormonal status are major determinants of drug addiction, and highlight the need to include both males and females in studies of addiction.

There have been several recent reviews on animal models of particular characteristics of addiction such as escalation of drug intake (Ahmed, 2009; Edwards and Koob, 2013), drug seeking (Mantsch et al., 2016; Marchant et al., 2013; Venniro et al., 2016), incubation of drug seeking/relapse vulnerability (Li et al., 2015; Wolf, 2016), enhanced motivation for drug (Allain et al., 2015; Oleson and Roberts, 2008), as well as reviews on methods used to induce one or more features of addiction in certain populations of animals (Ahmed, 2012; Belin-Rauscent et al., 2016; Deroche-Gamonet and Piazza, 2014; Waters et al., 2014). There have also been several recent reviews detailing sex differences in the behavioral and neurobiological mechanisms of addiction as a function of stage of the addiction process (Becker et al., 2017; Becker and Koob, 2016; Bobzean et al., 2014; Carroll and Lynch, 2016). In this review, the focus is on the procedures that have been used to study the five commonly modeled features of addiction with the goal being to provide a better understanding of the conditions needed to optimize their development in the majority of animals. Sex differences, and other individual differences, are also discussed for each feature since a better understanding of these differences is essential for our understanding of sex and individual differences in the development and treatment of addiction in humans.

2. Animal models of escalation/binge patterns of use

A loss of control over use and the excessive use of the drug, two defining features of human drug addiction, have been modeled in animals using several different extended access drug self-administration procedures (Ahmed and Koob, 1998; Allain et al., 2015; Balster and Woolverton, 1982; Fitch and Roberts, 1993; Lynch and Carroll, 2001). Early studies in non-human primates and rats showed that these characteristics are readily observed when animals are allowed continuous 24-h/day access (fixed ratio 1 schedule) to intravenous infusions of cocaine, methamphetamine, heroin, morphine, and phencyclidine infusions (Balster and Woolverton, 1982; Bozarth and Wise, 1985; Deneau et al., 1969; Johanson et al., 1976). Animals self-administering psychostimulants, such as cocaine, demonstrate periods of erratic and rapid drug intake interspersed with periods of self-imposed abstinence (Bozarth and Wise, 1985; Deneau et al., 1969) Animals self-administering opioids, such as heroin, progressively increase their drug intake over time to high levels (Bozarth and Wise, 1985; Balster and Woolverton, 1982). However, toxicity can develop rapidly under these conditions with these types of drugs, thus necessitating the use of conditions that restrict access in some way. Other drugs, such as nicotine and ethanol, can be available under unlimited-access conditions with limited toxicity (Balster and Woolverton, 1982; Valentine et al., 1997; Wolffgramm and Heyne, 1995).

Numerous methods have been developed to balance levels of intake and toxicity, particularly for psychostimulant and opioid drug self-administration (for review see Ahmed, 2009, 2012; Allain et al., 2015; Edwards and Koob, 2013; Roberts et al., 2007). For example, high levels of drug intake can be maintained with low levels of toxicity under continuous 24-hr/day access conditions when low drug doses are available (Carroll and Lac, 1997), when the total number of days is limited (3 days, Tornatzky and Miczek, 2000), or when the drug is self-administered orally rather than intravenously (Alexander et al., 1981; Barros and Miczek, 1996; Meisch, 2001). High levels of drug intake with limited toxicity can also be maintained under extended access conditions that restrict the total number of infusions available each day (Henry and Howell, 2009; Peoples et al., 1997), the total number of hours of access each day (6–12 h/day; Ahmed and Koob, 1998; Edwards and Koob, 2013; Mandt et al., 2015; Panlilio and Goldberg, 2007), that use a higher work requirement (e.g., fixed ratio 16; Carroll et al., 2005), or that include a time-out after each delivery (e.g. 15-min; Hutsell et al., 2016a, 2016b).

The most well established extended access drug self-administration procedure is the long access procedure developed by Ahmed and Koob (1998). With this procedure, animals are given continuous access to the drug for 6- to 12-hr/day. Under these conditions, animals self-administer high levels of the drug with few signs of toxicity. This procedure has also been shown to induce escalation of drug intake, or a progressive increase rates and levels of drug intake over time, which is not observed in control animals given short access to the drug (1–2-hr access/day). Drug use escalation has been observed for rats self-administering numerous drugs of abuse including cocaine, methamphetamine, synthetic cathinones or “bath salts”, heroin, oxycodone, and fentanyl (Edwards and Koob, 2013; Nguyen et al., 2017; Wade et al., 2015). Drug use escalation has also been observed in non-human primates for oral phencyclidine self-administration (Carroll et al., 2005), and in mice for intravenous oxycodone self-administration using modified access conditions (i.e., 4-hr/day access; Zhang et al., 2014). Escalation of alcohol and nicotine use has also been observed, although its occurrence may depend on the use of cyclic access conditions that alternate between periods of continuous access (12 to 24 h) and withdrawal (Carnicella et al., 2014; Cohen et al., 2012), or vulnerable populations of animals (i.e. alcohol preferring animals, Becker and Ron, 2014). Importantly, a history of escalating drug self-administration has been shown to lead to the development of other core characteristics of addiction including enhanced drug-seeking and its incubation over