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## Sex as a biological variable: Drug use and abuse

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### ABSTRACT

The study of sex as a biological variable is a necessary emphasis across a wide array of endpoints, including basic neuroscience, medicine, mental health, physiology and behavior. The present review summarizes work from clinical and preclinical populations on sex differences in drug use and abuse, ranging from initiation to escalation/dysregulation and from drug cessation/abstinence to relapse. These differences are analyzed in the context of the addiction cycle conceptualization of Koob and his colleagues and address patterns of drug use (binge/intoxication), motivation underlying its use (withdrawal/negative affect) and likelihood and causes of craving and relapse of drug taking (preoccupation/anticipation). Following this overview, an assessment of the basis for the reported sex differences is discussed in the context of the affective (rewarding and aversive) properties of drugs of abuse and how such properties and their balance vary with sex and contribute to drug intake. Finally, the interaction of sex with several experiential (drug history) and subject (age) factors and how these interactions affect reward and aversion are discussed to highlight the importance of understanding such interactions in predicting drug use and abuse. We note that sex as a biological variable remains one of critical evaluation and that such investigations of sex differences in drug use and abuse continue and be expanded to assess all facets of their mediation, including these affective properties, how their balance may be impacted by the multiple conditions under which drugs are taken and how this overall balance affects drug use and addiction vulnerability.

### 1. Goal

The goal of the present review is straightforward, i.e., to address sex as a biological variable in drug use and abuse. As such, we describe a myriad of differences between males and females from both clinical and preclinical populations in relation to the initiation, escalation, cessation/abstinence and relapse of drug taking. In so doing, we expand on a number of excellent reviews on this topic [1–8] and describe the relative roles of the rewarding and aversive effects of drugs as they contribute to various patterns of drug intake [9,10]. With that said, there are some preliminary issues that need to be addressed that qualify the major items listed in our stated goal, i.e., the characterization of drug use and abuse, the definition of sex differences and the strengths and limitations of clinical and preclinical models.

### 2. Preliminary caveats

#### 2.1. Drug use and abuse

Drug taking is not a unitary phenomenon and discussing any variable such as sex in this behavior requires an understanding of its

complexities. When examined over its progression, drug taking can refer to a variety of behaviors, i.e., its initiation, escalation, cessation/abstinence and finally relapse. Understanding the nature of, and processes involved in, the progression, including the basis for the differences in how individuals move through the stages of drug taking, will be important to predicting use and abuse potential. A conceptualization of this complexity has recently been introduced in a model by Koob and his colleagues [11,12] that describes drug use in terms of an addiction cycle of three distinct components: 1) binge/intoxication, 2) withdrawal/negative affect and 3) preoccupation/anticipation. Together, these components model patterns of drug-taking behavior, the motivational factors involved in drug use and abuse and the role of various environmental cues mediating relapse.

#### 2.1.1. Binge/intoxication

The binge/intoxication component focuses on the actual pattern of drug taking itself and reflects use that is either controlled or dysregulated. In the early use of the drug, intake may be limited and controlled (and possibly of long duration in individuals who take small amounts infrequently over many years, e.g., chippers); in later stages, intake may be more binge like with higher levels, greater frequency and extended

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durations.

### 2.1.2. Withdrawal/negative affect

The withdrawal/negative affect component refers to the consequences of drug use. In the initial use of the drug, the effects of drug taking are generally described in terms of some positive affect (reward) that reinforces drug taking and the cessation of drug taking is relatively neutral and has no affective consequence. With increased amounts and more frequent and extended drug use, there are neuroplastic adaptations in specific parts of the brain, e.g., mesolimbic and mesocortical pathways, thought to mediate drug reward such that the drug's rewarding effects are reduced or eliminated. Further, given these compensatory adaptations in various reward systems (as well as the recruitment of other pathways involved in stress reactivity, e.g., extended amygdala), animals are anhedonic in the absence of the drug (withdrawal; negative affect) that drives more drug taking. With this pattern of drug intake, the drug no longer produces positively rewarding effects (or such effects are significantly reduced) and drug use is maintained by negative (and not positive) reinforcement.

### 2.1.3. Preoccupation/anticipation

The final preoccupation/anticipation component refers to craving and relapse and focuses primarily on environmental triggers that reinstate or recreate drug-taking behavior. In the initial (limited) patterns of drug use, there is little craving for the drug (although there may be a desire to recreate the positively rewarding effects it produces). With extended intake (higher doses, more frequent use and longer duration), yet other brain systems, e.g., anterior cingulate cortex, dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, orbitofrontal cortex, are affected and/or recruited that mediate drug-, cue- and stress-induced relapse that reinstates use.

This addiction cycle illustrates how initial limited and controlled drug use reinforced by the drug's positive effects and with minimal or neutral affect in the drug's absence transitions to a pattern of extended use reinforced by withdrawal relief and stress reduction and reinstated by a host of environmental events. Important for the current review, any assessment of sex differences in drug-taking behavior must be viewed in this context of a moving target that may be controlled by different reinforcers (positive and negative), mediated by different brain areas and subject to differential control by environmental cues. Given that each of these factors may differ between males and females [1], an understanding of how sex interacts with (or is controlled or mediated by) these factors is critical to predicting sex differences in use and abuse.

## 2.2. Definition of sex differences

Becker and colleagues [1,2] have recently argued that sex differences are also a multifaceted issue and that males and females may differ in a number of ways on various behavioral and physiological endpoints. For example, sex differences may be either qualitative or quantitative. Qualitative differences refer to those in which males and females display fundamentally different behavioral responses, e.g., prepubertal gonadectomy lowers cocaine-induced motor activity in females and increases this activity in males [13], while quantitative differences reflect instances in which males and females may differ to varying degrees on some specific measure, e.g., the levels of stress associated with nicotine withdrawal (females > males) [14]; the effects of amphetamine on dopamine release in the ventral striatum (males > females) [15]. Males and females can differ at the population levels as well in that the number of males and females may vary on some behavioral endpoint, e.g., proportion of male and female rats acquiring cocaine self-administration (females > males) ([16]; see [17] for a discussion of how sex specific drug sensitivity contributes to such population differences); proportion of males and females using recreational drugs in the past month (males > females) [18]. Equally

important are instances in which males and females do not differ (qualitatively, quantitatively or proportionally), yet the similarities in responding may be mediated by differential underlying mechanisms [2]. Independent of the direction of the sex difference or its qualitative, quantitative or proportional characteristics, such assessments need to be multifaceted to address the complexity of comparisons between males and females. Further (and similar to investigations characterizing the different components of drug use and abuse; see above), understanding this complexity should shape research strategies to understand the extent, etiology and nature of such differences.

In addition to the multifaceted nature of sex differences as described above, studying sex differences in humans is made more complex, and has even been described to be confounded, by the concept of gender [19]. Where biological sex is genetically determined, gender is a concept that encompasses both biological sex and social constructs ultimately referring to which sex the individual identifies [20]. This identification can align with an individual's biological sex, i.e., a cis-gender individual [21], or it can be opposite to an individual's biological sex, i.e., a transgender individual [22]. Although the issue of gender is important in assessing behavioral and physiological differences among individuals, the use of gender as a factor in drug addiction is limited and the vast majority of clinical research on drug use and abuse classify subjects as male or female without specifying gender identification. Interestingly, the limited literature on gender and drug use suggests that transgender individuals display a greater risk of substance use and abuse than cisgender populations [23–26], clearly indicating that future research should seek to further understand gender identification in use and abuse vulnerability. Given the clinical literature reviewed in the current paper generally referenced biological sex as the variable under investigation, discussions of this literature in the review will address differences in biological sex unless gender was specifically identified as a factor (see [27]).

## 2.3. Strengths and limitations of clinical and preclinical models

Assessments of sex differences require both clinical and preclinical models, primarily due to the types of questions that can (and should) be asked of each population. For example, clinical models assessing drug use and abuse in humans have the clear advantage of studying the human condition and the possible cultural, social and economic factors that might differentially impact males and females [28–31]. Further, the types of questions one can ask of clinical populations include not only those regarding patterns of and motivations for drug use but also those addressing the efficacy of cognitive and behavioral strategies for treatment [32–34]. Conversely, human drug taking is difficult to track prospectively in individuals, thereby limiting information on transitions from initial to escalated drug use and from abstinence to relapse. Further, although assessments of the hormonal and/or neurobiological substrates of drug taking (see [35–39]) as well as evaluations of the impact of multiple factors such as stress (see [40]) can be done in humans, they may be limited by ethical concerns. Studying clinical populations clearly has the most translational application to human drug use, yet the very cultural, social and economic factors that one can study in this population may interact with various biological factors that are thought to be important in drug taking, making it difficult to assess their specific roles (see above discussion on gender identification; see also [2,3]). Finally, issues such as polysubstance use, stress, psychiatric illnesses and other disease comorbidity also complicate the identification and characterization of sex differences in clinical populations.

Although much is gained from clinical assessments of sex differences in drug use and abuse, questions remain that require preclinical research utilizing a variety of animal models (for reviews on animal models, see [41,42]). Such research enables assessments of the developmental and progressive aspects of addiction and the evaluation of a host of factors that are difficult to manipulate in humans. Preclinical

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