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Do initial responses to drugs predict future use or abuse?

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Abstract

DE WIT, H., T.J. Phillips. Do initial responses to drugs predict future use or abuse? Individuals vary in their initial reactions to drugs of abuse, in ways that may contribute to the likelihood of subsequent drug use. In humans, most drugs of abuse produce positive subjective states such as euphoria and feelings of wellbeing, which may facilitate repeated use. In nonhumans, many drugs initially increase locomotor activity and produce discriminative stimulus effects, both of which have been considered to be models of human stimulant and subjective states. Both humans and nonhumans vary in their sensitivity to early acute drug effects, in ways that may predict future use or self-administration, and some of these variations appear to be genetic in origin. However, it is not known exactly how the initial responses to drugs in either humans or nonhumans relate to subsequent use or abuse. In humans, positive effects of drugs facilitate continued use of a drug while negative effects discourage use, and in nonhumans, greater genetic risk for drug intake is predicted by reduced sensitivity to drug aversive effects; but whether these initial responses affect escalation of drug use, and the development of dependence is currently unknown. Although early use of a drug is a necessary step in the progression to abuse and dependence, other variables may be of greater importance in the transition from use to abuse. Alternatively, the same variables that predict initial acute drug effects and early use may significantly contribute to continued use, escalation and dependence. Here we review the existing evidence for relations between initial direct drug effects, early use, and continued use. Ultimately, these relations can only be determined from systematic longitudinal studies with comprehensive assessments from early drug responses, to progression of problem drug use. In parallel, additional investigation of initial responses in animal models as predictors of drug use will shed light on the underlying mechanisms.

Keywords

drug abuse; initiation; acute drug effects; predictors; risk; human; nonhuman

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1. Introduction

Most drugs of abuse produce subjective feelings of well-being and euphoria in humans, which are thought to contribute to the drugs' potential to be used or abused (de Wit and Griffiths, 1991; Fischman and Foltin, 1991). Indeed, drug-induced changes in mood or subjective state have long been the primary indicator of abuse potential used by the Food and Drug Administration (FDA) to assess the likelihood of abuse for new medications (Jasinski, 1991; FDA guidelines in Balster and Bigelow, 2003; Carter and Griffiths, 2009). Drugs that produce euphoria are more likely to be abused than drugs that fail to produce euphoria, and *individuals* who report experiencing more positive effects from a drug are more likely to use the drug again. However, the extent to which either the quality or magnitude of responses to the first few exposures to a drug are indicators of the individual's likelihood of continued use, or in the longer term to abuse or dependence, remains to be determined. The full clinical manifestation of drug dependence results from dynamic changes that occur only after repeated administration of the drug, including alterations related to learning, tolerance, cognitive function, stress, sensitization and complex neuroadaptations underlying these phenomena (Everitt et al., 2008). Thus, the relationship between early subjective responses and fully developed dependence is at best indirect (Wagner and Anthony, 2002). Yet, there is evidence that an individual's initial responses to drugs may constitute one factor contributing to the risk for future abuse or dependence. This is of particular interest because of the possibility that genetic factors may influence these initial responses, and thus impart vulnerability to future use.

2. Individual differences in responses to drugs

Individuals may differ in their responses to drugs on several dimensions, any of which may influence subsequent use. Individuals may differ in how the drug makes them feel (i.e., the subjective self-reported states in humans; discriminative stimulus effects in animals), how it affects physiological processes (e.g., heart rate; body temperature) or how it affects their behavior (e.g., risk-taking behavior in humans; locomotor activation or depression in rodents). Further, responses to drugs may vary in magnitude (i.e., greater or lesser sensitivity), the quality of effects (e.g., stimulant-like or sedative-like), the affective valence of the effects (e.g., liking, disliking), and the time course (e.g., onset or duration). These variations in acute drug effects may be genetic or nongenetic in origin. Further, several of these dimensions have been implicated in the etiology of drug abuse or dependence. For example, Conrod et al. (2001) suggest that the amount of increase in heart rate after alcohol is a positive indicator of risk for abuse, and Schuckit (1987) and others have suggested that low level of intoxication-like response to alcohol is a risk factor for future alcohol dependence (e.g., Conrod et al., 2001; Schuckit, 1987). Evidence for the causal role of these potential predictors is difficult to obtain in humans. In nonhumans, there is also a literature examining the relation between initial responses to drugs and future drug self-administration (see below). Advantages of the animal models include the degree of control over the animals drug use history, and the capacity to manipulate genetic variables. Although a comprehensive review of the nonhuman mammalian literature is beyond the scope of the present analysis, we note some interesting similarities between humans and nonhumans. It is also important to mention that a potential source of variability affecting both initial responses to drugs and progression to use is variation in the pharmacokinetic properties of a drug. For example, there is genetic variation in the rate at which certain drugs are metabolized, which may affect sensitivity to drug effects and either increase or decrease their risk for using the drug (Edenberg, 2007; Ho and Tyndale, 2007). The most common example of this factor is in the flushing response to alcohol, which decreases risk for developing alcoholism (see below).

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2.a. Methods for studying the role of initial responses in humans

Information about the relationship between sensitivity to initial drug effects and subsequent use in humans can be obtained from several sources, including retrospective studies with established drug users, longitudinal studies with early drug users, and laboratory-based studies involving drug choice. In retrospective studies, drug abusers are asked to recall their early drug use experiences (e.g., Haertzen et al., 1983). For some drug classes, these retrospective studies provide the only available source of information (e.g., opiate drugs in opiate abusers). However, retrospective studies are limited by their reliance on memory and highly selective bias in respondents, who are usually drug users with many years of drug experience. In prospective studies, initial responses to drugs are assessed in young early or non-users, and then their recreational use is followed over months or years (e.g., studies of early cigarette smokers (Chen et al., 2003; described below)). These studies are especially valuable because they provide a measure of initial drug response, not biased by memory. However, they are expensive and time-consuming, and are not possible for certain drug classes (e.g., illicit opiates). A further limitation of both retrospective and longitudinal studies is that initial drug effects are experienced under naturalistic conditions where expectancies, other concurrent drug use, and context can influence the apparent drug effect. In contrast, in human laboratory studies, participants receive controlled doses of drugs and are then allowed to consume and regulate their intake of the drug (Chutuape and de Wit, 1994; de Wit, 1998). These studies often document the participants' first experience with the drug, unconfounded by expectancies or contextual factors. Participants who report experiencing positive subjective drug effects (e.g., liking or euphoria) typically choose to consume the drug when given the opportunity. This concordance provides support for the idea that greater positive acute effects predict repeated use of the drug within the laboratory setting, and perhaps outside the laboratory as well. The measures of subjective drug effects are sensitive and reliable. Yet, in the context of opiate drugs, McAuliffe (1975) noted that subjective drug experiences are sometimes difficult to define, and subjects' ratings of positive effects such as 'euphoria', 'intoxication', 'high' and 'liking' of the drug, may not be readily distinguishable from their ratings of apparently negative effects such as 'nausea', 'sick', 'heavy'. Further, especially in the context of initially unpleasant drugs, users may 'learn to get high', and adapt to unpleasant side effects of the drug with repeated use. Thus, initially unpleasant subjective responses to certain drugs may become positive after relatively few uses.

2.b. Methods for studying the role of initial responses in nonhumans

Several experimental approaches have been taken to study the relationship between initial drug effects and use in nonhumans. Individual variation in sensitivity to initial drug effects (e.g., locomotor behavior, sedative effects) can be examined in relation to likelihood of initiating drug intake or amount consumed (e.g., Piazza et al., 1989; Pierre and Vezina, 1997). These studies provide some evidence that initial drug responses predict future use. However, many of the existing studies used genetically heterogeneous populations (parallel to unselected populations of humans), making it difficult to discern the specific roles of genetic and non-genetic factors in sensitivity. Moreover, these studies sometimes entail some initial drug exposure to identify a predictor trait, and this exposure itself could affect the subsequent intake measure. An alternative approach to studying the relation between initial drug responses and drug intake, which avoids this problem, is to utilize genetically defined types of animals to examine genetic correlations between acute drug responses and drug self-administration (e.g., Kamens et al., 2005). For example, this approach can be taken using panels of inbred mouse and rat strains, selectively bred lines of rodents and animals in which single genes have been manipulated. These studies may reveal common genetic factors that influence both initial sensitivity and drug intake.

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3. Specific examples of acute responses predicting use or abuse

The extent to which sensitivity to acute drug effects in humans predicts the trajectory of drug use outside the laboratory remains to be determined. Clearly, a multitude of other factors contribute to the etiology of drug abuse and dependence, including non-drug-related factors such as stress and impulsivity, and drug factors that only come into play after repeated ingestion of the drug in a specific context such as conditioning, tolerance and sensitization (Everitt et al., 2008). Recognizing that the initial reaction to a drug is but one of many factors that contribute to compulsive drug use, we evaluate evidence in humans and nonhumans that the initial drug effects contribute to subsequent regular use of alcohol, nicotine, cannabis, cocaine, caffeine and opiates. These drugs are included because they are among the most commonly used or abuse drugs for which pertinent data are available. Other drug classes, such as hallucinogens, benzodiazepines, barbiturates, inhalants and dissociative anesthetics will not be discussed because there is not enough information available.

We review evidence from both humans and nonhuman models. The concordance from human to nonhuman findings depends on the sensitivity and validity of the nonhuman models used. As noted in several recent reviews examining the consilience between rodent models and human measures of sensitivity to alcohol or nicotine (Crabbe et al., 2010; O'Dell and Khroyan, 2009; Stephens et al., 2011), there is a need for more refined measures in animals to match the measures used with humans. Nevertheless, we review the existing evidence from the nonhuman models to address the specific question, i.e., do initial responses to drugs predict future use? This information will provide a context for studying variability in early drug responses, related to both genetic and non-genetic factors, in relation to continued use (e.g. Haberstick et al., 2011; Lott et al., 2005).

3.a. Alcohol

3.a.i Evidence from humans—One well-documented source of variation in acute responses to alcohol stems from metabolic differences related to enzymes involved in the degradation of alcohol (Edenberg, 2007). Certain individuals, notably those of East Asian descent, experience an aversive facial flushing response after consuming alcohol, a response that can also include nausea, discomfort and tachycardia. The response is due to accumulation of the metabolite acetaldehyde, which can occur either from more rapid oxidation of alcohol by alcohol dehydrogenase (ADH) or from slower oxidation of acetaldehyde by aldehyde dehydrogenase (ALDH). Several genetic variants have been identified that affect both of these enzymes, and individuals affected by the flushing response have a markedly lower probability of developing alcoholism, presumably because of the aversive effects they experience after consuming alcohol (Edenberg, 2007; Whitfield, 2002).

There is also well-described individual variation in the pharmacodynamic profile of alcohol. Most of the studies that have examined acute responses to alcohol as predictors of future alcohol use focus on young adults with a family history of alcoholism but who have not yet themselves developed the disorder. Alcohol abuse and dependence are highly heritable, such that children of alcoholics are 4–5 times more likely to become alcoholic themselves (Schuckit, 1985a). The processes that mediate this risk are not understood, but one approach has been to compare responses to an acute dose of alcohol in individuals with or without a family history of alcoholism, while they are young and presumably at risk but not yet dependent. Schuckit and his colleagues have conducted an elegant series of studies addressing this question, demonstrating that sons of alcoholics exhibit a distinctive "low level of response" to certain effects of alcohol (Schuckit, 1984a, 1984b, 1994). They found that sons of alcoholic fathers report less subjective intoxication and body sway after a moderate dose of alcohol than men without alcoholic relatives. These at-risk individuals also

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exhibit less alcohol-induced body sway (Schuckit, 1985b; 1988), smaller alcohol-induced alterations in cortisol, prolactin, and ACTH levels, less intense changes in the P300 waves of event and differential EEG effects (Ehlers and Schuckit, 1990; Schuckit, 1988; Schuckit et al., 1987a, 1987b; Schuckit and Gold, 1988). The reduced level of response also occurs in daughters whose fathers have a history of alcohol dependence (Eng et al., 2005). From these data, Schuckit and colleagues proposed a *low-level response theory*. Individuals who are insensitive to these effects of alcohol are postulated to be more susceptible to future alcohol use, and ultimately abuse, because they are unable to gauge their own level of intoxication, and because they need greater amounts of alcohol to achieve the desired effects. In support of this idea, Schuckit (1994) conducted a 10-year follow-up study showing that a low response to alcohol predicted a four-fold increase in likelihood of developing future Alcohol Dependence (APA, 1994). These studies indicate that lesser responses to alcohol, including certain subjective and physiological responses, represent a risk factor not only for alcohol use, but also for future alcohol abuse or dependence. However, as noted next, alternatives to this theory have also been proposed.

An alternative to Schuckit's low-level response theory was proposed by Newlin and Thomson (1990), and recently re-examined by Newlin and Renton (2010). These authors cite 36 studies in which high-risk family history positive individuals demonstrated *higher* levels of early alcohol response compared to low-risk groups, on measures ranging from subjective reports of alcohol effects (e.g., stimulation, intoxication), to physiological effects (e.g., heart rate and cortisol) and behavioral measures (e.g., memory impairment). The authors noted that the studies that reported greater effects typically measured responses very soon after drug administration (sooner than most of the Schuckit studies), and thus proposed a *differentiator model*, that high-risk individuals have greater stimulant-like effects from alcohol during the ascending limb of the breath alcohol curve and less sedative-like effects during the descending limb. Thus, the models are consistent, but the differentiator model takes into account the biphasic nature of alcohol's effects. The relative predictive value of these proposals (low level response vs differentiator model) will be resolved with further, in-depth longitudinal studies.

Taken together, these studies with alcohol provide some support for the idea that variations in initial responses to alcohol can predict levels of future alcohol use. Yet, the findings are complex and sometimes conflicting. Acute alcohol effects that are clearly unpleasant (e.g., flushing) appear to discourage drinking. Either greater stimulant effects or lesser sedative effects appear to predict escalation of drinking. Notably, however, alcohol challenge studies in the United States typically include participants 21 and older, whose responses may already be influenced prior experience. Assessing responses to alcohol at an earlier age would provide more accurate measure of biological response and potential risk. Indeed, to the extent that early age of onset of drinking is a predictor of future abuse (Grant, 1998; Moss et al., 2007), the first experiences of greatest importance may occur much earlier than 21 years of age. It is not even known whether acute response to alcohol is systematically related to age during the early, vulnerable ages. Another limitation to the human alcohol challenge studies is that most studies have tested healthy, young, usually Caucasian, volunteers without psychiatric or other substance disorders. Considering the prevalence of psychiatric comorbidity between alcohol dependence and other psychiatric conditions, it would be of particular interest to examine early responses to alcohol among individuals with psychiatric disorders or dysregulated HPA function. It is also likely that there are multiple trajectories to alcohol dependence such as the type 1 higher functioning, environmentally influenced alcoholism, and the type 2 male-predominant familial, severe alcoholism characterized by onset before age 25 (Cloninger et al., 1981). A recent large-scale study suggested that there are as many as five different subtypes, each with a distinctive etiology and trajectory (Moss et al., 2007). Initial reactions to alcohol may play a different role in

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these subtypes (e.g., Gordh et al., 2011). Future research on the relation between initial alcohol responses and alcohol use disorders may help to refine these subtypes and their biological mechanisms.

3.a.ii Evidence from nonhumans—In nonhumans, metabolic factors have also been considered. An Aldh type 2 knockout mouse that has high acetaldehyde levels in blood, brain and liver after alcohol exposure (Isse et al., 2005), exhibits a reduced preference for alcohol (Isse et al., 2002). Further, alcohol has differential effects on Aldh type 2 gene expression in different strains of mice, that correspond with their differences in alcohol preference, indicating a genetic correlation between these traits. A more modest correlation was found between Adh type 1 gene expression and alcohol preference in these mouse strains (Tagliabracci and Singh, 1996). However, the role of these enzymes in the brain appears to be more complicated, as there is also evidence that these alcohol metabolizing enzymes in the brain may play a positive role in the reinforcing effects of alcohol (Karahanian et al., 2011). These authors suggest that alcohol serves as a prodrug for acetaldehyde, and that acetaldehyde serves as the active reinforcing drug. This builds on an older literature suggesting that acetaldehyde plays a role in alcohol self-administration (e.g., Amit et al., 1977). In addition, metabolites of alcohol, such as acetate, may be another source of variation in sensitivity to aversive effects of alcohol that influences alcohol consumption (Maxwell et al., 2010).

The animal alcohol literature provides mixed support for the idea that alcohol sensitivity is associated with level of alcohol use. As with the human findings just described, sensitivity in animals is not a singular concept, and has been measured in many ways. For example, one commonly used measure of alcohol sensitivity in animals is locomotor activity. Alcohol can either increase or decrease locomotor activity, depending upon the dose of alcohol and the time after alcohol administration at which behavior is measured. Mice bred to have a greater locomotor stimulant response to alcohol early after administration (Crabbe et al., 1987; Phillips et al., 2002) consume more alcohol (Risinger et al., 1994). To the extent that locomotor activity represents stimulant-like positive effects, this is consistent with the idea that greater sensitivity to positive stimulant effects of alcohol predicts more alcohol use. However, consistent with both the differentiator and low level of response models, the higher alcohol consuming line of mice are less sensitive to the sedative-hypnotic and some ataxic effects of alcohol (Shen et al., 1996; Phillips et al., 2002; but see Boehm et al., 2000). In addition, using data from several laboratories collected in a panel of inbred rat strains, a correlational approach and subsequent factor analysis offered some support for a relationship between higher alcohol intake and lower initial sensitivity to sedative-intoxicating effects of alcohol (Spuhler and Deitrich, 1984). These findings, taken together with data from inbred mouse strains, examining sensitivity-intake relationships (Ozburn et al., 2010; Crabbe et al., 2010) provide inconclusive evidence for the relation between initial stimulant effects and subsequent alcohol consumption.

Lines of mice and rats have also been bred for their large differences in alcohol consumption, but the findings have again been mixed, with regard to their initial sensitivity to alcohol. The low level of response relationship with high intake has received some, but not perfect, support for some sedative and ataxic effects of alcohol (Colombo et al., 2000; Crabbe et al., 2010; Files et al., 1996; Kurtz et al., 1996; Lumeng et al., 1982; Phillips and Crabbe, 1991; Schechter, 1992). Also, a relationship of a greater stimulant response with higher alcohol drinking has sometimes been supported (Agabio et al., 2001; Krimmer, 1992; Krimmer and Schechter, 1992; Quintanilla, 1999; Rodd et al., 2004; Waller et al., 1986), but in other cases has not (Grahame et al., 2000; Paivarinta and Korpi, 1993; Phillips et al., 2005; 1995). Some of the disparity is likely due to the genetic heterogeneity of alcohol drinking, something that must be considered in outcomes from both humans and

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nonhumans. For example, gene-specific research has identified mechanisms that could underlie a relationship between alcohol sensitivity and consumption (e.g., Hodge et al., 1999; Kim et al., 2011; Naassila et al., 2002; Thiele et al., 2000). However, correspondence of sensitivity with consumption, not surprisingly, has not found for all genetic manipulations that have been examined (Crabbe et al., 2006).

In rodent studies, conditioned aversive effects of alcohol assessed soon after administration are negatively correlated with consumption. Lines of rats and mice that were bred for higher levels of alcohol consumption also exhibit reduced sensitivity to the conditioned aversive effects of alcohol (Chester et al., 2003; Froehlich et al., 1988; Quintanilla et al., 2001), and conversely, animals bred for greater conditioned aversion consumed less alcohol (Phillips et al., 2005). Similar results have been found in pairs, panels and crosses of inbred strains (Broadbent et al., 2002; Horowitz and Whitney, 1975; Ozburn et al., 2010; Risinger and Cunningham, 1992; however, see Cailhol and Mormede, 2002; Risinger and Cunningham, 1998). In general, although exceptions can be found in the literature, the data suggest that there is a genetic relationship between these traits, and that sensitivity to the aversive effects of alcohol serves as a protective factor against excessive alcohol intake. In humans, the initial aversive effect of alcohol has not been systematically studied as a predictor of future use, except in the context of the flushing response in Asians.

In nonhumans, information about the interoceptive effects of alcohol, or how alcohol makes animals “feel”, is obtained using drug discrimination methods. In these studies, the animal indicates whether an ingested or injected solution “feels” (or tastes) like alcohol or not, usually by pressing an alcohol-associated or non-alcohol-associated lever. The findings from these studies examining the quality and magnitude of interoceptive effects of alcohol in relation to the propensity to self-administer alcohol have been mixed (Gordon et al., 1993; Krimmer, 1992; Krimmer and Schechter, 1992; McMillan and Li, 1999, 2001; McMillan et al., 1999; York, 1981). However, it was recently shown that chronic exposure to the stress hormone corticosterone blunted the ability of rats to identify alcohol (Besheer et al., 2011). This is consistent with the idea that chronic stress may reduce the subjective effects of alcohol in humans, leading an individual to consume more alcohol to achieve the desired effect.

3.b. Nicotine

3.b.i. Evidence from humans—Nicotine is a particularly interesting and paradoxical case for examining the idea that initial, acute responses to drugs predict progression to repeated use. Nicotine (or tobacco) is unique among other drugs of abuse in that its initial subjective effects are typically not pleasant, and indeed often include unpleasant experiences such as nausea and dizziness. As a result, it is often thought that early use of tobacco is determined more by environmental influences (e.g., peer pressure) than by pleasant pharmacological effects. Eissenberg and Balster (2000) reviewed the literature on early responses to tobacco in relation to risk for regular smoking. Their review included both retrospective studies assessing memories of early responses among individuals who have tried smoking, as well as longitudinal studies assessing early responses to smoking among pre-adolescents and adolescents. There are several more recent longitudinal studies, and there is also epidemiological evidence relating cigarette smoking to variations in enzymes involved in the metabolism of nicotine.

Several retrospective studies have examined participants’ recollections of their initial responses to smoking, as possible predictors of progression. Haertzen et al (1983) conducted an early retrospective study with opiate abusers who were asked to recall their early experiences with nicotine and other drugs. Whereas they reported pleasurable initial responses to heroin and cocaine which, they claimed, influenced subsequent use, they

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remembered experiencing mainly unpleasant initial effects from tobacco, and that these effects were unrelated to their subsequent smoking. In their review of initial response as predictor to smoking Eissenberg and Balster (2000) found mixed results: In some studies fewer dysphoric effects from initial cigarettes predicted smoking, whereas in other studies more positive effects predicted future smoking. More recently, DiFranza et al (2004) interviewed 237 seventh graders who had ever inhaled tobacco smoke, regarding their initial sensitivity to effects of nicotine. Relaxation was the strongest predictor of progression to subsequent smoking, but surprisingly and counter-intuitively, nausea, or dizziness also independently predicted progression. Similarly, Chen et al (2003) surveyed 610 10th grade students who had ever tried smoking. After controlling for age and gender, pleasurable cigarette smell, pleasurable buzz/rush, relaxation and dizziness predicted continued smoking. The finding that pleasant cigarette smell was a predictor is interesting in light of preclinical evidence that nicotine may enhance the value of environmental stimuli that have some motivational value because of their association with primary rewards (Caggiula et al., 2009; Chaudhri et al., 2006). Alternatively, it is possible that cigarette smell was pleasant because of previous associations with smoking (e.g., parents who smoked). Whether these remembered initial responses to smoking were accurate, and whether they were causally related to progression, cannot be determined from these retrospective studies.

Several prospective studies have examined the relation between initial sensations and later dependence. DiFranza et al (2007) studied 217 6th graders who had ever inhaled tobacco smoke, and followed them for 4 years. They found that feelings of relaxation after initial smoking predicted nicotine dependence, or “loss of autonomy over smoking” and dependence (WHO, 1992) four years later. Other predictors were familiarity with popular cigarette advertisements (e.g., Joe Camel), novelty seeking and depressed mood. Kandel et al (2007) conducted a 2-year longitudinal study with 353 6th to 10th graders who had tried a cigarette within the year before the study or during the study. About 25% of the sample developed Nicotine Dependence (APA, 1994) over a two-year period, and pleasant initial sensitivity to tobacco smoke was among the best predictors of developing dependence. These authors took care to obtain ratings of pleasantness and unpleasantness with regard to sensations such as dizzy, rush, and buzz, and concluded that sensations that were regarded as pleasant were most predictive. Several other studies have reported similar results (Audrain-McGovern et al., 2007; Hu et al., 2006). More recently, Buchmann et al (2011) followed a cohort of German adolescents who had ever tried smoking, from age 15 until 22, to identify determinants of progression. They found that earlier age of smoking was associated with more pleasurable sensations from the first cigarette and, although both predicted progression to regular smoking, the age of smoking initiation was the more robust predictor of progression to dependence. The question of whether the subjective or behavioral effects of acute nicotine, or other drugs, vary with age, especially at younger ages, is of critical importance and may explain differences in vulnerability. Unfortunately, ethical concerns about administering drugs to children and adolescents make it unlikely that these important studies will be done. Taken together, however, the prospective studies that have been conducted add to the evidence that initial responses to nicotine contribute to the likelihood of escalation from use to dependence.

Perkins and colleagues have studied subjective responses to acute nicotine in relation to consumption in controlled studies in healthy volunteers (Perkins et al., 2001; 2000; 2008). In one study (Perkins et al., 2001), nonsmokers sampled a nicotine nasal spray, and then had the opportunity to ingest it again. Subjects who reported more positive effects from the spray were more likely to take it again, whereas subjects who experienced negative effects were less likely to take it again. In another study (Perkins et al., 2008), they examined subjects’ responses to intranasal nicotine in relation to retrospective reports of early smoking experiences. Adult nonsmokers who had smoked only 1–10 times in their lifetime and

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remembered feeling dizzy and buzzed from their first cigarette also reported these same effects after receiving nicotine in a nasal spray. They described the effects as unpleasant, which may have contributed to their non-continuation of smoking.

As is the case for alcohol, pharmacokinetic factors may influence rates of smoking, and perhaps early responses to smoking (Audrain-McGovern et al., 2007; Ho and Tyndale, 2007). The metabolic inactivation of nicotine is controlled by genes such as CYP2A6 that encodes a hepatic enzyme that affects most of the metabolism of nicotine to cotinine (Benowitz and Jacob, 1994). Some studies have reported that variations in this gene predict nicotine dependence: Slower metabolizers, who have genetic variants associated with less than half of the activity of normal metabolizers, smoke fewer cigarettes and are less likely to be current smokers (Malaiyandi et al., 2006). However, this genetic relationship has not always been found (Carter et al., 2004). Whether metabolic factors play a role during early smoking experiences remains to be determined. Audrain-McGovern et al (2007) examined the role of pharmacokinetic variation in early onset of smoking, in adolescents from grades 9 to 12. Normal metabolizers progressed to nicotine dependence at a faster rate than slow metabolizers, and these increases in nicotine dependence leveled off more slowly compared with slower metabolizers. However, they found that initial subjective experiences from smoking were not related to the genotypes, nor were they predictive of nicotine dependence.

Thus, the studies with early responses to nicotine provide mixed evidence for the relation between early acute response and smoking progression. Some studies found that initial feelings of relaxation or pleasurable buzz predicted progression, whereas others found that dizziness and even nausea predicted future smoking. Yet other studies found that early responses that were unpleasant decreased the likelihood of progression. These highly variable findings suggest that early positive subjective responses to nicotine may play a minor role in the development of smoking, and that perhaps magnitude of any subjective response (positive or negative) may be predictive. Alternatively, other factors related to context, learning and neurobiological adaptations may be more important for this drug.

3.b.ii. Evidence from nonhumans—In animals, nicotine also has competing positive and aversive effects. Nicotine self-administration in animals has typically been studied using intravenous (IV) methods, and dose-response curves for IV self-administration have typically been inverted U-shaped, reflecting lower dose positive effects through higher dose aversive properties. Nicotine self-administration has been demonstrated in several species (e.g., mice—Stolerman et al., 1999; rat—Corrigall and Coen, 1989; Brower et al., 2002; dog—Risner and Goldberg, 1983; nonhuman primate—Sannerud et al., 1994). However, few studies have examined the relationship between initial sensitivity to nicotine and nicotine intake. Recent reviews (Changeux, 2010;Tuesta et al., 2011) nicely detail current knowledge about the involvement of specific nicotinic receptor subtypes, signaling mechanisms and brain locations in nicotine, as well as other drug, self-administration behavior, but does not touch on the topic of initial sensitivity. However, there are genetic differences in sensitivity to behavioral effects of nicotine (Bergstrom et al., 2003; Boyle and Gill, 2009; Gill and Boyle, 2005; Marks et al., 1989; Overstreet, 1995; Tritto et al., 2004; 2002), which may affect self-administration. Using inbred mouse strains varying in sensitivity to the first dose of nicotine, Robinson et al (1996) examined whether initial sensitivity corresponded with oral self-selection of nicotine, when the animals were offered the choice of a nicotine-containing solution vs. water or saccharin water. They found a strong negative genetic correlation between nicotine intake and sensitivity to nicotine-induced seizures, suggesting that sensitivity to an apparently aversive effect of nicotine may limit intake. This relationship deserves further more careful study in animal models.

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As in the studies with humans, pharmacokinetic factors may also affect nicotine self-administration in mice. Mice with greater CYP2A5 protein levels (homologous with human CYP2A6 protein), suggestive of an increased rate of nicotine metabolism, showed increased nicotine self-administration (Siu et al., 2006). In addition, rats of the Lewis strain have been found to self-administer more nicotine than rats of the Fischer 344 strain, and they also appear to have a more rapid nicotine clearance curve, and perhaps higher initial peak levels of nicotine (Sziraki et al., 2001).

3.c. Cannabis

3.c.i. Evidence from humans—Both retrospective and prospective studies have examined the relationship between initial responses to cannabis and subsequent use of marijuana. Davidson and Schenk (1994) queried 197 college students about memories of their initial experiences with marijuana, using a questionnaire describing both positive and negative effects. Respondents who experienced more positive effects from the drug the first time had a shorter latency to their second use as well as higher lifetime use. Although only a few respondents reported negative effects from the drug, these negative ratings did not predict use. Le Strat et al (2009) conducted a retrospective analysis of 1472 young cannabis users in New Zealand and France to investigate the positive and negative effects of cannabis at first use in relation to cannabis dependence at age 18–21. Participants rated the number of positive experiences from the cannabis at initial use, from 1 to 5 positive responses (e.g., feeling high or happy). The study found that the odds ratio of developing cannabis dependence among respondents who reported 5 positive effects was 28 times that of becoming dependent with no initial positive effects, although the categorical classification of ratings limits the conclusions that can be drawn. Ferguson et al (2003) conducted a longitudinal study of 198 respondents who had used cannabis before age 16, again using the ratings of 1–5 positive experiences. Participants who reported 5 positive responses to cannabis at initial use had an odds ratio of 28.5 for becoming dependent 4 years later, compared to respondents who reported no positive effects. As in the Davidson and Schenk study, negative experiences were unrelated to future use, Taken together, these studies suggest that positive subjective responses to initial marijuana experiences are predictive of future use. It should be noted, however, that many factors influence subjective responses to drugs, especially marijuana, including expectancies (Kirk et al., 1998), prior drug use and personality (Chait and Perry, 1992). Thus, although early ratings of liking marijuana appear to predict future use, the extent to which this is based on the pharmacological response is not known. This would only be answerable with controlled studies in which the drug could be administered for the first time under double blind conditions, which is unlikely to occur. This problem with expectances also applies to the first use of other classes of drugs in a naturalistic situation, where users almost always have expectancies regarding the drug's identity and its effects.

3.c.ii. Evidence from nonhumans—The natural cannabinoid, delta(9)-tetrahydrocannabinol (THC), and synthetic and endogenous cannabinoid receptor agonists such as, WIN 55212-2 and anandamide, are self-administered by animals (monkeys—Justinova et al., 2008; Tanda and Goldberg, 2003; Tanda et al., 2000; rats—Fattore et al., 2001; Lecca et al., 2006; mice—Mendizabal et al., 2006). However, some have argued that cannabinoids are atypical in preclinical animal models with regard to their profiles as drugs of abuse, because the experimental conditions under which motivational and reinforcing effects are displayed are more restricted than for other drugs of abuse (Panagis et al., 2008). Stimulant and depressant responses to acute cannabinoids have been recorded (Bass et al., 2002; Darmani, 2001; Meschler et al., 2000; Varvel et al., 2007; Wiley et al., 2008), as have aversive effects (McGregor et al., 1996; Murray and Bevins, 2010). Further, the role of endogenous endocannabinoids and their receptors more generally in drug reinforcement and

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other addiction-related behaviors (Serrano and Parsons, 2011), and in stress associated responses (Dubreucq et al., 2011; Riebe and Wotjak, 2011), has more recently received considerable attention. However, the question of whether initial sensitivity to cannabinoids predicts level of cannabinoid intake does not appear to have been addressed in animal models of cannabinoid use. This is perhaps partly because self-administration of cannabinoids has been more difficult to reliably establish in animal models compared to self-administration of most other addictive drugs.

3.d. Cocaine and other stimulants

3.d.i. Evidence from humans—A few retrospective studies have examined initial response to cocaine or other stimulants as a predictor of future use. In one early study (Haertzen et al., 1983) opiate abusers claimed that initially positive responses to cocaine predicted their later use of the drug. Davidson et al (1993) interviewed 44 college students who reported having used cocaine and found that positive responses to the drug on initial use predicted a shorter latency to the second use. Negative effects did not predict future use. More recently, Lambert et al (Lambert et al., 2006) conducted a study with 202 adults who had tried cocaine at least once between ages 16–40. Participants who reported 'liking' and 'wanting' the drug upon initial exposure to cocaine were more likely to develop cocaine dependence and life-time cocaine abuse.

Many laboratory-based studies have examined subjective responses to stimulant drugs such as amphetamine and methylphenidate in healthy volunteers, in relation to consumption or choice (Chait, 1993; de Wit et al., 1986; Holdstock and de Wit, 2001; Johanson and Uhlenhuth, 1980; Kollins et al., 2001; Lott et al., 2005; Rush et al., 2001; Volkow et al., 1999). Healthy young adults vary in their ratings of arousal, liking and anxiety after low doses of amphetamine. These studies consistently show that pleasurable, stimulant-like subjective effects are directly related to consumption of the drug, within the experimental context. In the studies with amphetamine, most participants experience positive mood effects from amphetamine during their first experiences with them, but a small minority experience unpleasant effects such as anxiety. The mood effects of the drug clearly predict whether subjects will choose to take the drug again when they are given the opportunity, on subsequent study sessions. These studies provide strong support for the idea that pleasurable initial responses are related to subsequent drug-taking, albeit in the limited context and abbreviated time frame of a laboratory research study. These acute drug challenge studies may help to identify risk factors predicting future use, including genetic factors (Lott et al., 2005), personality and psychiatric symptoms (de Wit and Bodker, 1994; de Wit et al., 1987), expectancies (Mitchell et al., 1996) and brain dopamine receptor density (Volkow et al., 1999). The studies show systematic relations between acute drug responses and drug choice in the laboratory.

3.d.ii. Evidence from nonhumans—In rats, using genetically heterogeneous groups of animals, locomotor response to an acute dose of a psychostimulant may predict consumption of the drug. For amphetamine, greater acute sensitivity to locomotor effects of the drug was associated with higher levels of self-administration (Deminiere et al., 1989; Piazza et al., 1989). This relationship has also been found for cocaine in some, but not all, studies (Mandt et al., 2011; 2008; Mantsch et al., 2001). When approaches have been used that directly investigate potential genetic relationships between sensitivity and intake, evidence has also been mixed. In a panel of inbred mouse strains, postprandial drinking of cocaine and sensitivity to the stimulant effects of cocaine were not strongly related (Seale and Carney, 1991). However, in rat lines selectively bred for high vs. low locomotor activity in a novel environment, the high activity line rats exhibited a higher propensity to self-administer cocaine (Cummings et al., 2011; Davis et al., 2008) and greater sensitivity to quinpirole

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(Flagel et al., 2010), a dopamine D2/D3 receptor agonist, which would be thought to partly mimic the effects of cocaine. Unfortunately, to the best of our knowledge, drug sensitivity has not been fully characterized in these lines, although one study showed no difference between the lines in activation to an initial treatment with a 15 mg/kg dose of cocaine (Garcia-Fuster et al., 2010). A mouse line selectively bred for higher oral intake of methamphetamine (Shabani et al., 2011; Wheeler et al., 2009) that also exhibits greater operant methamphetamine self-administration (Shabani et al., 2012a) exhibit greater acute locomotor activation to methamphetamine (Shabani et al., 2011). However, mice bred for extreme sensitivity to the stimulant effects of methamphetamine voluntarily consume *less* methamphetamine compared to the oppositely selected low stimulation line (Kamens et al., 2005). The authors suggest two interpretations. First, the mice bred for high stimulation may require less MA to experience rewarding effects and thus, may choose to consume less MA compared to the mice bred for low stimulation. Alternatively, extreme sensitivity to the stimulant effect could be aversive, and thus, avidity for methamphetamine is reduced. The positive association of methamphetamine intake and stimulation in the lines bred for high and low MA drinking was seen only at a higher 4 mg/kg dose, whereas the stimulation selected lines were bred based on their response to 2 mg/kg methamphetamine. It is possible that the use of the lower dose resulted in a more profound sensitivity, as one would expect to identify more sensitive animals with this low dose, than with a higher dose.

In addition to the association of sensitivity to stimulant effects with intake, aversive effects of methamphetamine have been studied. Mice bred for low drinking of methamphetamine solutions showed profound conditioned aversion induced by a single treatment with methamphetamine that was not seen in the high line mice, even after multiple treatments (Shabani et al., 2012b; Wheeler et al., 2009). These results are similar to those for alcohol, and suggest that high sensitivity to the aversive effects of methamphetamine protects against high levels of intake.

Another source of information about initial responses to drugs and drug-taking in animal models comes from studies of discriminative stimulus effects. For example, rats that were more sensitive to the activating effects of amphetamine were also more sensitive to its discriminative stimulus effects (Bevins et al., 1997). In a study in non-human primates investigating cocaine self-administration and drug discrimination, at least one dose supported only self-administration without serving as a discriminative stimulus. This suggests that cocaine reinforcement can occur in the absence of a cocaine-like discriminative stimulus effect (Martelle and Nader, 2009). However, once a drug has been established as a discriminative stimulus, it can substantially increase subsequent self-administration (Panlilio et al., 1996). Thus, sensitivity to drug discriminative stimulus effects has the potential to influence drug intake.

3.e. Caffeine

3.e.i. Evidence from humans—In an early retrospective study, Haertzen et al (1983) queried opiate abusers about their initial responses to caffeine. Although these participants claimed that their initial responses to heroin and cocaine predicted subsequent use of these drugs, they reported that their initial responses to caffeine were unpleasant and not related to future use. To our knowledge, no longitudinal studies have examined the initial responses to caffeine in relation to future use. One challenge to conducting longitudinal studies on early responses to caffeine is that caffeine use begins early (Frary et al., 2005), usually in the form of caffeinated sodas. Because of the widespread use of these drinks and the relatively subtle acute effects of low doses of caffeine, it is difficult to assess early responses under non-controlled conditions.

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Several laboratory-based studies have examined acute subjective responses to caffeine in adults as predictors of choice or consumption of the drug in the laboratory (Griffiths and Woodson, 1988; Stern et al., 1989). These studies support the idea that pleasant caffeine-induced effects such as mental arousal and decreased fatigue predict drug choice, whereas unpleasant effects such as jitteriness or anxiety predict non-choice of caffeine. There is also indirect evidence that negative subjective responses predict low caffeine use. Patients with Panic Disorder experience anxiety from caffeine, and consume less of it than healthy controls (Boulenger et al., 1984; Charney et al., 1985; Lee et al., 1988; Uhde et al., 1984). Moreover, in both Panic Disorder patients and healthy controls, individuals with a certain polymorphism of the adenosine receptor gene are more likely to experience anxiety from an acute dose of the drug (Alsene et al., 2003; Charney et al., 1985; Childs et al., 2008; Lee et al., 1988; Uhde et al., 1984). Yang et al (Yang et al., 2010) recently reviewed evidence for the contribution of genetic factors in responses to caffeine in humans and found evidence for genetic contributions to the positive vs negative subjective or physiological effects of caffeine (e.g., feelings of arousal, anxiety or insomnia), level of habitual caffeine consumption and caffeine metabolism. Indeed, recent genome-wide association analyses involving thousands of people have identified significant associations with caffeine intake for single nucleotide polymorphisms that suggest a role for genes involved in the metabolism of caffeine or the constituents of coffee (Amin et al., 2011; Cornelis et al., 2011; Sulem et al., 2001). Whether there is a role for these genes in caffeine sensitivity has not been explored.

3.e.ii. Evidence from nonhumans—Relatively few studies have examined initial acute responses to caffeine in relation to self-administration in nonhumans. However, mechanistic studies point to a role for the A_{2A} receptor subtype in both caffeine consumption and locomotor activation (El Yacoubi et al., 2000; 2005; Yang et al., 2009), using A_{2A} knockout mice. In another study using A_1 knockout mice, no evidence for a role of the A_1 receptor subtype in caffeine consumption was found (Rieg et al., 2007) and a lesser role than that of the A_{2A} receptor was found for caffeine-induced locomotor stimulation (Yang et al., 2009). Though these are interesting results that suggest some common mechanisms underlying sensitivity and intake, they do not directly address the question of whether initial sensitivity to caffeine predicts future intake.

3f. Opiates

3.f.i. Evidence from humans—In an early retrospective study, Haertzen et al (1983) reported that opiate abusers liked their first experiences with heroin and other opiates more than they liked 11 other types of drugs that they had used, and that opiates were their preferred and primary drug of choice from the beginning. Conducting a retrospective study that included non-drug-abusing volunteers, Bieber et al (2008) recruited 20 opioid abusers in a treatment center and 20 controls, all of whom had first received opiates for pain control. Participants completed a retrospective questionnaire reporting the feelings of euphoria and well being they experienced upon their first use of an opiate drug. The drug-abusing participants reported having experienced greater euphoria upon their first use than the control group. There are no longitudinal studies on initial responses to opiates in relation to subsequent abuse, although such information would be valuable because of the widespread medical use of opiates as well as the recently increasing prevalence of abuse (Manubay et al., 2011; Maxwell, 2011). Fortunately, only a very small proportion of patients who receive opiates for pain control progress to develop problems with abuse (Hojsted and Sjogren, 2007). Controlled studies with healthy volunteers do indicate that acute responses to opiates vary markedly across individuals (Comer et al., 2010; Lasagna et al., 1955; McAuliffe, 1975; Zacny and Gutierrez, 2003; Zacny et al., 1994; 1992), from pleasant to unpleasant.

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Whether these initial subjective effects of opiates predict repeated use or choice over a placebo has yet not been studied.

3.f.ii. Evidence from nonhumans—The question of the relationship between initial sensitivity and self-administration of opiates has received relatively little attention in nonhuman studies. C57BL/6J inbred strain mice exhibit a larger initial stimulant response to morphine than do DBA/2J mice (Belknap et al., 1989), and DBA/2J mice exhibit a locomotor depressant response to morphine early after administration (Phillips et al., 1994). Consistent with the idea that stimulation is related to reward, morphine supports intravenous self-administration in C57BL/6J, but not DBA/2J mice (Elmer et al., 2010). These data are in agreement with two-bottle choice drinking studies showing greater morphine consumption in the C57BL/6J than DBA/2J strain (Belknap et al., 1993; Horowitz et al., 1977). Thus, for these two strains, the data suggest that greater initial sensitivity to stimulant effects of an opioid is associated with greater reinforcement, and greater sensitivity to depressant effects reduces consumption. However, in another set of 4 strains, oral self-administration of the opioid, etonitazene, was not associated with sensitivity to etonitazene-induced locomotor stimulation or other effects (Elmer et al., 1995). A few studies in single gene mutant mice are also relevant. Not surprisingly, mu-opioid receptor knockout mice do not self-administer morphine and show reduced sensitivity to morphine-induced locomotor stimulation (Sora et al., 2001). In mice lacking protein kinase C epsilon, increased susceptibility to morphine self-administration was associated with enhanced sensitivity to morphine's analgesic effects, compared to their non-mutant counterparts (Newton et al., 2007). Mice lacking the NK1 receptor, the preferred receptor for substance P, exhibited heightened sensitivity to locomotor depressant effects of morphine, as well as reduced self-administration of morphine (Ripley et al., 2002). These results mirror those for DBA/2J, compared to C57BL/6J, mice. Overall, the data support a positive relationship between sensitivity to stimulant effects of opioids and opioid self-administration and a negative relationship between sensitivity to depressant effects of opioids and opioid self-administration.

4. Conclusions

We have reviewed evidence examining the relationships between early responses to drugs and progression to continued use, abuse and dependence (as appropriate) in humans and nonhumans. There is little question that there are marked individual differences in acute responses to drugs, and there is some evidence that some of these differences are genetic. Certain direct effects of drugs are clearly protective against future use, such as, in humans, the flushing response to alcohol and perhaps the anxiety response to caffeine. Other direct effects, such as euphoria and stimulation, appear to facilitate repeated use across several classes of drugs, including opiates and stimulants, although the evidence in animals is more mixed for stimulants. Overall, initial positive or negative effects of drugs probably influence the likelihood of continuing use, at least in the short term. The relationship between early direct responses and dependence, however, is less clear. To the extent the early use must precede escalation of use and dependence, there is likely to be some relation between initial responses and dependence. However, the contribution of the initial acute effect of the drug is probably minor, compared to the multitude of other variables that contribute to excessive drug use. These include cognitive factors related to decision-making, physiological factors related to stress, and the processes of learning, tolerance, sensitization, and physical dependence that only develop with continued ingestion of the drugs.

We have identified gaps in the literature, methodological challenges and directions for future research. Longitudinal research documenting initial drug effects, and following probands across their drug-taking trajectories, is the gold standard. Longitudinal studies would be of

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particular interest with opiates, for example, and with cigarette smokers. Animal models also offer a valuable tool for studying this relationship, and for particular studying genetic factors. Initial drug responses can easily be obtained in naïve animals, genetic characteristics and context can be controlled and drug dose and purity are not an issue. Relatively few nonhuman studies have followed the complete time progression of the dependence process, beyond the initial self-administration period. To coordinate the human and nonhuman studies, there is a need to develop and refine drug-abuse related measures that are directly comparable in humans and animals (Crabbe et al., 2010; O'Dell and Khroyan, 2009; Stephens et al., 2011). Although the relationship between initial drug sensitivity and risk for abuse or dependence is not likely to be simple, further exploration is likely to solidify which traits are of greatest relevance and thus, of greatest predictive value.

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Highlights

- We review evidence that initial responses to abused drugs predict progression in use.
- We consider findings with humans, as well as nonhumans, and several classes of drugs.
- Some genetic factors influence both initial drug responses and drug consumption.
- Procedures assessing comparable drug responses in humans and nonhumans are needed.