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William L. Woolverton: A Case History in Unraveling the Behavioral Pharmacology of Stimulants

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Abstract

Clinical findings suggest that the most promising strategy for cocaine addiction is a combination of indirect-acting monoamine agonists with some form of behavioral intervention. This approach can be traced back to preclinical research, some of which was conducted by William L. Woolverton. The goal of this brief review is to provide readers with an appreciation for the experimental breadth involving both behavior and pharmacology that encompassed Woolverton's amazing career, from the evaluation of abuse liability of drugs to the use of complex behavioral contingencies to better model the human condition. We begin with Woolverton's research using simple and complex schedules of reinforcement to evaluate abuse liability and how that has impacted current animal models. We also discuss his use of cocaine vs. food choice schedules of reinforcement as a model to evaluate potential medications for treating cocaine use disorders. Woolverton concluded that drug taking behavior was not "impulsive" and "out of control" as has often been proposed, but rather directly determined by the environmental contingencies and the context of its availability, providing a nuanced understanding of drug-behavior interactions.

Keywords

Dopamine; Cocaine; Drug Self-Administration; Drug Choice; Rhesus Monkey

INTRODUCTION

The 2012 Monitoring the Future Study in the United States reported that about 3 to 8% of 12th graders surveyed used cocaine or amphetamine in the past year. Approximately 1.6

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million individuals aged 12 or over were cocaine users (SAMHSA, 2013; Gerlach et al., 2014). Unlike alcoholism, opiate addiction and cigarette smoking, there are currently no FDA-approved pharmacotherapies for cocaine, MDMA or methamphetamine use disorders (Phillips et al., 2014). While pharmacotherapies alone lack proven efficacy, the combination of drug treatment with behavioral interventions has shown the most promise (e.g., Brady et al., 2011; Sofuoglu et al., 2013; Phillips et al., 2014). As will be described below in greater detail, William L. Woolverton spent most of his professional career as a leader in combining pharmacology and behavioral contingencies to better understand cocaine self-administration using nonhuman primates. The use of agonist pharmacotherapies and contingency management can be traced back to his pioneering research. Many of the papers included in this Special Issue are written by scientists influenced by Woolverton and include much of Woolverton's preclinical research, therefore those details will not be repeated in this paper. For this review, we will highlight two facets of Woolverton's career: the importance of the schedule of reinforcement used in drug self-administration studies and the emphasis on environmental contingencies and their ability to alter drug self-administration.

Model development

Many animal models of drug abuse utilize self-administration under simple schedules of reinforcement, especially fixed-ratio (FR) schedules. However, the development of cocaine pharmacotherapies will require more translational animal models to the human condition. Many of Woolverton's major scientific contributions identified and characterized the behavioral determinants of the abuse-related effects of drugs. In addition to the drug choice and progressive-ratio studies that will be described later, Woolverton was interested in developing homologous animal models of drug addiction. For example, one of the clinical symptoms of withdrawal from a cocaine binge is the "crash" (Gawin and Kleber, 1986) including symptoms such as depression, fatigue, agitation and anhedonia; however, demonstrating this withdrawal symptom in animal models (rodent and nonhuman primates) has proven difficult (Carroll and Lao, 1987). When monkeys were given unlimited access to self-administer cocaine their behavior was similar to the binge pattern seen in heavy and dependent cocaine users, including periods during which drug taking is voluntarily discontinued (Deneau et al., 1969; Johanson et al., 1976; Aigner and Balster, 1978). Unfortunately, by modeling the human condition in this manner, the behavioral baseline was highly variable making it difficult to study, and importantly, the animal's health was also compromised. Woolverton and Kleven (1988) designed an experiment that involved high doses of investigator-administered cocaine and examined the effects on food-maintained lever pressing. They reported that (1) tolerance developed to the response rate-disrupting effects of cocaine, similar to tolerance development seen in people, and (2) discontinuation of cocaine administration produced a transient disruption in food-maintained responding. There were several implications from this early study that continue to move the field forward. Although tolerance to the euphoric effects of cocaine are believed to be one mechanism mediating continued drug use, tolerance to the reinforcing effects of cocaine in animal studies is not reliably shown (e.g., Nader et al., 2006). Yet, Woolverton and Kleven (1988) did report tolerance to the disruptive effects of cocaine which may allow users to self-administer more drug over time contributing to the escalating pattern of use that is often seen. As described below, Woolverton's study involving procaine and other local anesthetics

was an example of his ability to combine pharmacology and behavior to better understand the factors mediating cocaine's high abuse potential (Woolverton, 1995).

Early in his career, Woolverton carried out a very interesting series of studies of the self-administration of local anesthetics other than cocaine. Procaine, a local anesthetic, was shown to maintain self-administration when studied under simple schedules of reinforcement (Ford and Balster, 1977). In fact, procaine was shown to maintain higher rates of responding than cocaine (Woolverton and Balster, 1979a, 1982), yet procaine abuse is very uncommon despite it being used to dilute cocaine for intranasal use. On the face of it, this would seem to be a “false positive” for the drug self-administration model. However, structure-activity relationships between the reinforcing effects and binding to the dopamine transporter of local anesthetics were a significant part of one of the early statements of the role of dopamine uptake inhibition as the neural basis of cocaine reward (Ritz et al., 1987).

Even though dopaminergic effects of local anesthetics appeared to be the basis for their reinforcing effects, Woolverton was determined to find a model that would be predictive of cocaine's much greater abuse liability than procaine and related drugs. He hypothesized that response rates leading to cocaine or procaine injections were not the optimal measure on which to compare their reinforcing strength. In fact, Woolverton (1995) stated “To measure reinforcing effects reliably, it would seem important to minimize the influence on responding of drug effects other than the reinforcing effect (e.g., direct effects on response rate, satiation, discriminative stimulus effects)”. The two models Woolverton used most frequently to study reinforcing strength were drug choice and progressive-ratio schedules of reinforcement.

In one study, Nader and Woolverton (1991) trained one group of monkeys to choose between procaine and food and another group to choose between cocaine and food. One goal of this choice study was to determine whether procaine choice was more sensitive than cocaine choice to manipulation of an alternative non-drug reinforcer. Increasing the magnitude of the alternative food reinforcer shifted the procaine dose-response curve down, while the same manipulations shifted the cocaine choice dose-response curve to the right (Nader and Woolverton, 1991). Woolverton concluded that the environmental manipulation affected the potency of cocaine as a reinforcer, as represented by a parallel shift in the cocaine dose-response curve, but decreased the efficacy (strength) of procaine, as represented by the flattening of the curve, and this outcome was consistent with the higher abuse liability of cocaine compared to procaine.

Food-drug choice studies are excellent models of human drug taking, as described in the next section, but the limitation is that they are not the ideal model to directly compare the reinforcing efficacy of a series of drugs because of the extended time necessary to train the animals. The progressive-ratio (PR) schedule of reinforcement, in theory, is better suited for comparisons of reinforcing efficacy of several drugs, allowing for structure-activity relationships using within-subjects design. But even responding under the PR schedule was shown to be influenced by schedule parameters, and parametric manipulations were needed to examine this relationship. True to Woolverton's commitment to understanding how these variables affect cocaine self-administration, he conducted several parametric studies

involving PR schedules of reinforcement (Woolverton, 1995; Rowlett et al., 1996). To complete the procaine example, Woolverton (1995) found that there were no statistically significant differences between cocaine and procaine when the inter-injection interval (i.e., timeout after an injection) was 15 minutes, but the break point (defined as number of injections) for cocaine was significantly higher than procaine when the inter-injection interval was 30 min. As Woolverton (1995) stated "Considered together, these results argue again for the importance of allowing drug effects to dissipate between injections in a procedure designed to measure reinforcing efficacy". These findings are consistent with drug-drug choice studies in which cocaine was chosen over procaine almost exclusively, even when the procaine dose was 16 times higher than the cocaine dose (Johanson and Aigner, 1981). Food-drug and drug-drug choice studies, along with progressive-ratio schedules used to assess reinforcing strength, have provided novel insights into the mechanisms of action mediating cocaine's high abuse liability and remain fundamental in preclinical abuse liability assessments, in general (e.g., Woolverton and Johanson, 1984; Lile et al., 2002; Ator and Griffiths, 2003; Carter and Griffiths, 2009; see Woolverton and Nader, 1990).

Role of dopamine receptors and environmental context in cocaine reinforcement

In 1984, Woolverton and colleagues investigated the role of dopamine (DA) D1- and D2-like receptors in maintaining intravenous drug self-administration by rhesus monkeys. They concluded that D2-like agonists (apomorphine, piribedil, propylbutyldopamine and bromocriptine) maintained self-administration when substituted for cocaine, but the D1-like agonist SKF38393 did not, apparently implicating D2-like, but not D1-like receptors in the reinforcing effects of cocaine. It would take years before it was determined that D1-like agonists could function as reinforcers, including in nonhuman primates (Weed and Woolverton, 1995) and that the tool available at the time, SKF38393, was actually a low-efficacy agonist. However, Woolverton did not wait for medicinal chemists and *in vitro* receptor pharmacologists to make these discoveries. In 1986 and 1989, he reported that DA receptor antagonists at both receptor families would decrease cocaine self-administration, thereby implicating both D1- and D2-like receptors in cocaine-maintained responding (Woolverton, 1986; Woolverton and Virus, 1989).

As highlighted earlier, Woolverton felt that the examination of agonists to assess reinforcing effects, as well as the use of receptor antagonists to better identify cocaine's mechanisms of action, both required self-administration conditions that went beyond simple schedules of reinforcement. As it relates to evaluating potential cocaine pharmacotherapies (especially DA receptor antagonists), drugs rarely decreased cocaine self-administration at doses that did not also decrease food-maintained responding (e.g., Herling and Woods, 1980; Woolverton and Virus, 1989). Because of these direct effects on behavior, Woolverton utilized other models of drug self-administration, and in this case food-drug choice schedules of reinforcement seemed the ideal baseline on which to evaluate treatments (e.g., Woolverton and Balster, 1979b, 1981).

In some of the first studies using complex schedules of reinforcement to evaluate pharmacotherapies (see Brady and Griffiths, 1976), Woolverton and Balster (1979b) trained

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rhesus monkeys to choose between cocaine and food reinforcement using a discrete-trials choice procedure. The frequency of cocaine choice over food was dose-dependent: low cocaine doses were chosen less than food, but higher cocaine doses were exclusively preferred to food reinforcers. This baseline allowed for the assessment of drug treatments that were not confounded by overall decreases in response rates. While there was some evidence of mutual antagonism of the behavioral-disrupting effects of high doses, drugs such as the D2-like receptor antagonist chlorpromazine and haloperidol did not decrease the percent of trials in which cocaine was chosen, nor did administration of those drugs result in a reallocation of responding to the non-drug food alternative (Woolverton and Balster, 1981). These findings parallel clinical studies showing that D2-like receptor antagonists do not decrease cocaine use (Gawin, 1986; Sherer et al., 1989; Ohuoha et al., 1997; Grabowski et al., 2000). The food-drug choice paradigm is widely considered the most appropriate model to evaluate pharmacotherapies (see Ahmed, 2010; Banks and Negus, 2012 for recent reviews) and there are data now suggesting that stimulating or antagonizing receptor subtypes of the D2-like family may be effective in decreasing cocaine choice relative to food reinforcers (e.g., Czoty and Nader, 2013).

While Woolverton was a pharmacologist by training, he had an incredible passion for understanding behavior and proudly described himself as a behavioral pharmacologist in the tradition of his mentors including Charles R. Schuster, Chris-Ellyn Johanson, Marian W. Fischman, and Robert L. Balster. This led him to conduct a series of studies involving food-drug choice conditions in which he systematically manipulated environmental variables (e.g., Nader and Woolverton, 1991, 1992a,b; Woolverton and Rowlett, 1998; Anderson et al., 2002; Woolverton, 2003; Woolverton et al., 2007, 2012; Freeman et al., 2012). Increases in the magnitude of food reinforcers could decrease cocaine choice (Nader and Woolverton, 1991), as could increases in the “cost” (FR value) of cocaine (Nader and Woolverton, 1992a; Negus, 2003). These environmental effects on cocaine choice were every bit as large as the effects of drug pretreatment in shifting the cocaine dose-response curve to the right. When a colleague mentioned to Woolverton that the effects of alternative reinforcers or response cost are “obvious”, he replied “we still have to demonstrate that these manipulations will decrease cocaine self-administration”. A great deal of recent research is focused on environmental conditions and the impact (both positive and negative) these variables have on cocaine self-administration in animal models (e.g., Bardo et al., 2013; Czoty and Nader, 2013; Lynch et al., 2013; Smith and Witte, 2012).

These early monkey studies on cocaine-food choice and environmental contingencies pioneered by Woolverton have translated to successful treatment outcomes in the face of no current FDA-approved medications. For example, it has been shown that contingency management – providing alternative non-drug reinforcers for cocaine-free urines has resulted in increased abstinence (Winhusen et al., 2012; Dunn et al., 2013; Higgins et al., 2014). Most recently, these alternative reinforcers have included employment opportunities (DeFulio and Silverman, 2011). A study involving work-release programs for prisoners found a similar positive outcome – provide alternative reinforcers (in this case a job) and drug use will decrease for a significantly longer period of time and, in many cases, remain low (Butzin et al., 2005; see also Bahr et al., 2010). As mentioned earlier, the combination of these behavioral interventions (contingency management and cognitive behavioral

therapies) with potential pharmacological treatments for which Woolverton contributed significantly, are showing the greatest benefit in treating cocaine abusers. Because there will probably be no pharmacological magic bullet for cocaine addiction, Woolverton's focus on individual subjects and environmental contingencies has proven to be highly translational. His inductive scientific approach followed in the traditions of B.F. Skinner, Murray Sidman, Joseph V. Brady, Travis Thompson and Charles R. Schuster, scientists whose work he so wonderfully carried forward. His work will be similarly carried forward in the ever-evolving scientific exploration of the behavioral pharmacology of drugs acting on the central nervous system.

Epilogue and Conclusion

Dr. William L. Woolverton, Billy S. Guyton Distinguished Professor and Vice Chair for Research in the Department of Psychiatry and Human Behavior at the University of Mississippi Medical Center died after a brief illness at the age of 62 on June 13, 2013. He was a scientist who stressed the importance of conducting research that was relevant to addressing real world challenges such as treating addiction. He was a humanitarian, a rock and roll guitarist who loved to explore venues for creative music (see Figure) as much as he loved scientific exploration. He made clear that the center of his life, however, was people, beginning with his wife Candy, son Chris and daughter Lucy, along with a long list of trainees, colleagues, friends, and extended family. His passion for science, his integrity and respect for all people he interacted with and his optimistic outlook on everything will be remembered by those fortunate enough to have known him. We, the field of behavioral pharmacology, and the world are better for his time with us.

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Highlights

- Nonhuman primate models of drug abuse
- Alternative reinforcers and drug choice: translational research
- Homologous animal models of cocaine addiction
- Combining drug treatments with environmental manipulations

Figure 1.
Bill Woolverton in front of the Poor Monkey Lounge in Merigold, MS, October 19, 2010.