Pharmacology, Biochemistry and Behavior xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Self-administration of methamphetamine aerosol by male and female baboons

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ARTICLE INFO

Keywords:
Methamphetamine
Baboon
Sex differences
Self-administration
Aerosol inhalation
Vapor inhalation
Smoking

ABSTRACT

The reinforcing efficacy of vaporized methamphetamine HCl (0.3 mg/kg) was determined in baboons with minimal previous drug exposure. A group of 8 adult male baboons was tested prior to a group of 7 adult female baboons. Baboons were initially trained to suck on a brass stem activating a pressure-sensitive relay (i.e., puff), to receive one M&M® candy. Five of the 8 males and 6 of the 7 females learned to activate the relay. 0.05 ml of 95% ethyl alcohol containing 0.3 mg/kg methamphetamine was vaporized and delivered to the mouth of the baboon after he/she completed 2 puffs; a single candy was given after an additional 5 puffs to ensure that baboons continued puffing after the aerosol entered their mouths. Puffing was recorded but not reinforced by candy or drug for 2 min after each aerosol delivery for males and 1 min for females. Males could earn 10 and females could earn 20 aerosol deliveries. Males made between 225 and 650 puffs each session. Females made between 200 and 400 puffs each session. When only candy and placebo aerosol were delivered the number of puffs decreased in all 6 females but increased in all 5 males. When candy was delivered without aerosol, puffing decreased in 4 of 5 males, but this manipulation was not tested in females. Methamphetamine aerosol delivery maintained lower rates of puffing behavior in females than males, but procedural differences weaken interpretation of this sex comparison. Although training non-human primates to inhale drug vapors is time consuming, if successful, their long lifespan could provide years of valuable data justifying further work with non-human primates using models of vaporized drug self-administration.

1. Introduction

Humans commonly inhale drugs by smoking drugs in cigarette forms (e.g., marijuana, tobacco) or by directly inhaling aerosols (e.g., heroin, THC, nicotine), yet compared to intravenous or oral routes of drug delivery, preclinical self-administration studies with non-humans using inhaled drugs are relatively few. Liquid aerosol is formed by heating a drug until it produces a vapor that upon rapid cooling condenses to form an aerosol (small liquid particles suspended in air; Wood, 1990). Aerosol production is possible for drugs that vaporize before they are pyrolized. Early studies examined the effects of the delivery of drug by combusting it in combination with plant material (see review by Wood, 1990). For example, Cole and colleagues trained 2 chimpanzees and 1 orangutan to inhale tobacco cigarettes containing methamphetamine (Pieper and Cole, 1973) or THC (Cole et al., 1971) by reinforcing the great apes with M&M® candy for successively longer puffs on a stem. Reinforcing long puffs with candy was effective in training great apes to “smoke” up to 8 tobacco cigarettes laced with methamphetamine or THC. This procedure was later used to train rhesus monkeys to puff on lettuce leaf cigarettes containing cocaine base (Siegel et al., 1976). Ando and Yanagita (1981) attempted to train 14 monkeys to self-administer, via puffing, tobacco cigarette smoke without any non-drug reinforcement and only 2 of the 14 animals acquired tobacco self-administration.

Studies looking at drug aerosols using rodents have relied most often on ventilated chambers such that drug aerosol can be delivered in a controlled manner and the animals will necessarily take drug as they breath (Wong, 2007). Such procedures have been commonly used to study the behavior or toxicological effects of inhaled chemical exposure (e.g., Phalen, 1997) and alcohol (e.g., O'Dell et al., 2004; Gilpin et al., 2008). Several early studies modified this approach to work with non-human primates. For example, in order to examine the behavioral toxicology of marijuana smoke, a large group of rhesus monkeys was exposed, via a face mask, to the smoke of marijuana cigarettes (e.g., Schulze et al., 1989; Slikker et al., 1991; Pryor and Rebert, 1989). In another early study (Katz et al., 1991), squirrel monkeys, who had been trained to discriminate intravenous cocaine from placebo, responded as if they had been given intravenous cocaine after exposure to vaporized

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https://doi.org/10.1016/j.pbb.2018.03.005
Received 29 November 2017; Received in revised form 6 March 2018; Accepted 12 March 2018

cocaine base in a ventilated chamber. These studies clearly demonstrated that inhalation of drug vapors and other components of some plant products produces significant behavioral effects.

While nicotine and cannabis are commonly smoked as plant material, other abused drugs are administered in a more direct form such as inhalants. Yanagita et al. (1970) demonstrated the reinforcing efficacy of chloroform, ether and lacquer thinner when delivered via indwelling intranasal cannulas in rhesus monkeys. Twenty years later, Carroll made significant contributions to the study of self-administered "smoked" drugs using a device similar to that used by Hatsukami et al. (1990) for delivering precise amounts of vaporized cocaine base to human cocaine smokers. Rhesus monkeys were trained to activate a pressure-sensitive relay in order to receive a single dose of cocaine base vaporized by rapid heating of a metal coil (Carroll et al., 1990), similar to the technology currently used in e-cigarettes (Harrell et al., 2014). Responding for cocaine was greater than for lidocaine, cocaine produced the expected physiological changes in heart rate (Carroll et al., 1990), response rates were increased, as observed with intravenous self-administration, when the monkeys were food deprived (Comer et al., 1995), and response rates were decreased by buprenorphine (Rodefer et al., 1997). Vaporized heroin was also self-administered under these procedures (Mattox and Carroll, 1996). Using this technology, 10 years later Newman and Carroll (2006) reported that rhesus monkeys who had been trained to self-administer cocaine base would self-administer methamphetamine: methamphetamine was less efficacious than cocaine and the dose-response function was relatively flat.

In a similar time-frame Lichtman, Martin and Boni developed devices that provided for aerosol delivery to mice either by generating the aerosol directly on a heating coil or pulling aerosol from lit marijuana cigarettes through a system connecting to a nose piece for mice (e.g., Lichtman et al., 1996, 2000, 2001). Using this system Meng et al. (1999) reported that methamphetamine aerosol and intravenous methamphetamine had similar pharmacokinetic profiles. More recently a similar system was used to deliver synthetic cannabinoids ("Spice") to mice (Wiebelhaus et al., 2012). While these systems deliver behaviorally active drug directly to a mouse's nose, the required restraint of the mouse limits its utility for self-administration studies. The current vaping technology that provides for rapid, precise and well controlled volatilization of drugs of abuse has led to a resurgence of work looking at the effects of inhaled drugs in laboratory rodents. Studies have demonstrated the utility of commercially-available vaporizers for the administration of nicotine (Lefever et al., 2017a), THC (Lefever et al., 2017b; Manwell et al., 2014a, 2014b), methamphetamine (Juarez-Portilla et al., 2017; Marusich et al., 2016; Nguyen et al., 2016b) and synthetic cannabinoids (Nguyen et al., 2016a) to rodents. Of note, Nguyen et al. (2016a) reported a decrease in intracranial self-stimulation threshold with inhaled methamphetamine and synthetic cannabinoids, which suggest that the aerosol would function as a positive reinforcer. Clearly, e-cigarette technology has been instrumental in conducting research with inhaled drugs and has opened up a wide range of opportunities for future research.

We have used a procedure for administering drug aerosols to rhesus monkeys that is based upon the way human cocaine users smoke cocaine. Monkeys activated a pressure-sensitive relay by puffing on a brass stem that was attached to a heated glass tube that contained stainless steel mesh. Upon completion of the response requirement drug dissolved in 95% ethanol was dropped onto the screen and vaporized such that continued puffing on the stem delivered drug aerosol. Four of six rhesus monkeys acquired heroin self-administration, developed a place-preference for the experimental space associated with heroin self-administration (Foltin and Evans, 2001) and chose heroin over a preferred fluid reinforcer during choice trials (Evans et al., 2003). The first purpose of the current study was to determine if this procedure could be used with another non-human primate species with a larger brain, the baboon, to engender methamphetamine self-administration. Baboons were chosen because of their utility in PET imaging studies (VandeBerg et al., 2009). If successful, the study would lay the foundation for future work with baboons that would allow PET imaging of receptor binding and neurotransmitter release as a function of aerosol inhalation. Of the studies involving non-human primates and inhaled drug self-administration cited in this paper, 120 males and 1 female (the sex of 9 additional animals was not specified) participated. Of the 15 studies involving rodents and inhaled drug self-administration cited in this paper only 1 study tested females. Clearly, there is a significant paucity of data on aerosol administration in females. Therefore, the second purpose of the current study was to compare methamphetamine aerosol self-administration between male and female baboons.

2. Method

2.1. Animals

One group of 8 adult male baboons (*Papio cynocephalus anubis*), initially weighing 19.8 to 26.5 (Mean = 23.6) kg completed the study and then a group of 7 adult female baboons, initially weighing 8.4 to 15.5 (Mean = 11.7) kg completed the study. All baboons had experienced acute (< 10) injections of intramuscular (i.m.) amphetamine and i.m. dexfenfluramine, while the males also had experienced acute (< 10) injections of i.m. heroin and i.m. naloxone. All baboons also had previous experience responding for food pellets or M&M® candy under a daily schedule similar to that described below. Baboons were individually housed in custom-designed non-human primate cages (1.4 × 1.2 × 1.5 m high) at The New York State Psychiatric Institute. The room was illuminated with fluorescent lighting from 7:00 AM to 7:00 PM daily. In addition to food and candy earned during experimental sessions, two chewable vitamins, two pieces of fresh fruit, and a dog biscuit were also given daily. Water was available ad libitum from a spout located at the back of each cage. All aspects of animal maintenance and experimental procedures complied with the U.S. National Institutes of Health Guide for Care and Use of Laboratory Animals, and were approved by the New York State Psychiatric Institute Animal Care and Use Committee.

2.2. Apparatus

Two response panels were located on the front wall of the cage. Six session lights (CM 1820, 24 V; Chicago Miniature, Buffalo Grove, Ill., USA) with white lenses were evenly spaced around the outside edges of each panel. From the baboon's perspective the right panel was used for food delivery, while the left panel was used for aerosol delivery. At approximately waist height for a sitting baboon the food panel had one Lindsley lever response manipulanda (BRS-LVE, Beltsville, Md., USA) mounted at the baboon's left and one mounted at the baboon's right. There were two stimulus lights mounted above each lever. A pellet dispenser (BRS-LVE model PDC-005) was also mounted on the outside of response panel with a tube that ran to a pellet catch cup that the baboons could reach into to pick up the food pellets. At approximately waist height for a sitting baboon the aerosol panel had one Lindsley lever, with a single light over it, mounted at the baboon's left. Two stimulus lights were mounted over a brass pipe mouthpiece that was at approximately mouth height for a sitting baboon at the baboon's right, i.e., lever to the left, stem to the right. A pressure-activated relay (Micro Pneumatic Logic, Fort Lauderdale, Fla., USA) signaled the computer whenever a monkey sucked on the pipe. A heated stem (Boni et al., 1991), similar to that used by humans when smoking cocaine (Foltin et al., 1990), was mounted on the outside of the aerosol panel. A glass tube (10 mm) fitted with a screen for holding drug was set inside another glass tube (12 mm) mounted on the outside of the panel. The external pipe was wrapped by a heating coil (Cole-Parmer Co., Vernon Hills, Ill., USA), encased in fiberglass insulation (Cole-Parmer) with temperature controlled with a heat controller (#515, George Ulanet Co., Newark, N.J., USA). The heat source was maintained at a