Animal Models of Drug Self-Administration by Smoking

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INTRODUCTION

Animal models of drug self-administration have made major contributions to understanding the behavioral and pharmacologic determinants of substance abuse practices. Intravenous (IV) administration has been the predominant route employed in such studies; the limited self-administration literature on organic solvents and volatile anesthetics demonstrates that the inhalation route is useful and practical. The literature on animal models of smoking is less persuasive because the experimental designs have been limited and because the technical challenges offered by these experiments can be substantial. Description of the dose delivered by smoking may be complex because of the number of compounds present and the differences in deposition and absorption associated with gases and particulates. The pattern of particulate deposition is species and particle-size dependent. Combustion products may be aversive because of eye or airway stimulation; behavior of the user may minimize aversive stimulation. In some species, the trigeminal reflex limits exposure to acutely aversive atmospheres. Combustion or pyrolysis need not occur if cocaine base is heated gently; the smoke observed under these conditions is a condensation aerosol that may not be aversive. Special generation techniques will be required to generate: (1) reliable exposure concentrations with stable particle size distributions; (2) test atmospheres of low irritancy that are appropriate for the species under study; and (3) exposures tailored specifically for studies of self-administration, behavioral and physiological effects, pharmacokinetics, or acute or chronic toxicity.

The chemicals subject to abuse by inhalation may be divided into two classes, those that are volatile at room temperature (inhalants) and those that require heat for self-administration, i.e., smoking. This chapter will examine the commonalities and differences between these substance abuse practices in a search for the major determinants of the process and for the implications for developing useful animal models of the process.

The inhalation route offers a number of advantages; only the simplest equipment is needed, no needles are required, and the rapid onset of effects is unmatched. A wide variety of chemicals are self-administered by inhalation. Inhalant abuse continues as an unrelenting substance abuse problem that is global in scope; organic solvents, fuels, gases, and volatile anesthetics continue to be abused to such an extent that the lifetime incidence of inhalant abuse among high school seniors ranks fifth behind alcohol, tobacco, marijuana, and stimulants. Smoked compounds include tobacco products (cigars, cigarettes, pipes), narcotics (opium, heroin), cannabis products (marijuana leaf, hashish, extracts), hallucinogens (dimethyltryptamine, the arylcyclohexylamines), and cocaine base (crack, freebase). A drug or chemical can be "smoked" if it displays substantial vapor pressure below temperatures at which pyrolysis occurs.

Forcible exposure to combustion products by chamber or tracheostomy are useful for some toxicologic purposes, but they yield no information on self-administration, and they may vary in their ability to provide adequate identification or characterization of the health consequences of smoking. The test atmospheres generated in such studies do not necessarily resemble the products generated by human smoking topographies, because the products of a burning cigarette are complexly determined, as are the properties of the aerosol (Davies 1988). In such studies, animals are exposed either continuously or during a fixed proportion of breaths, and the spectrum of toxic effects has been observed to differ from that in humans (Larson and Silvette 1971; Auerbach 1967; Hammond et al. 1970).

There are many anecdotal reports of animals that smoke. Darwin (1892) reports

Many kinds of monkeys will, as I have myself seen, smoke tobacco with pleasure . . . The same tastes are common to some animals lower in the scale. Mr. A Nichols informs that he kept in Queensland in Australia three individuals of the *Phascolarctus cinereus* [koala] that . . . acquired a strong taste for rum and smoking tobacco. (Darwin 1892, p. 7)

Tracheostomized dogs have been used extensively in studies of lung diseases induced by cigarette smoke, and the animals seem to adapt to these procedures quite well:

After a few weeks, the [tracheostomized] dogs became habituated to cigarette smoking and seemed to enjoy it as indicated by tail wagging and jumping into the 'smoking box' voluntarily. Thereafter, the use of the pump was discontinued and the dogs voluntarily inhaled smoke by drawing on the cigarettes . . . (Hammond et al. 1970, p. 742)

By and large as he becomes more used to the smoking, in humanoid fashion, he seems to relish the habit. (Cahan and Kirman 1968, p. 573)

The scientific literature on drug self-administration by smoking, however, is restricted and of limited value. There is no doubt that performances can be engendered that resemble human smoking topographies; monkeys can be trained to puff on cigarettes to obtain a liquid reinforcer, and this has been used as an exposure technique to study the various consequences of exposure to the test smoke atmosphere. Although these puffing performances can be characterized as response-produced exposures, they are not necessarily demonstrations of self-administration, i.e., behavior maintained by the drug as a reinforcer. Few studies have conducted any of the control procedures necessary to document self-administration (Pickens and Thompson 1968; Wood 1979). These control procedures include

- acquisition of an arbitrary response with access to the agent as the reinforcer,
- decrease in the frequency of the response when access to the purported reinforcer is discontinued;
- generation, by schedules of reinforcement, of typical patterns of behavior;
- maintenance by the agent of frequency of responding that is an inverted-U-shaped function of concentration; and
- discrimination by the subject between those responses that produce the agent and those that do not, that is, the behavior must not result from a general rate-increasing effect.

The last control procedure is a critical requirement, since a response-produced exposure to a psychoactive substance may increase its own frequency of occurrence. For example, an animal may develop a stereotypy on or have a seizure near the response sensor; in the case of puffing, the drug exposure may alter the frequency of oral activities.

Further information supports inhalation, but not self-administration. Patent compounds or metabolites in body fluids, such as, in cigarette smoking, the presence of large amounts of cotinine or nicotine in the urine, indicates inhalation, because the acidic smoke is not absorbed through the oral mucosa (Armitage 1970). For puffing response topographies, the volume of smoke drawn past the subjects lips should be greater than that of the buccal cavity and/or typical puffing responses. Finally, exposure-related physiological changes support inhalation, but provide no evidence of self-administration.

TOBACCO SMOKING MODELS

Several investigators have produced smoke puffing by encouraging animals to drink through a straw, i.e., to pull a column of water up from a reservoir, intermittently switching from water to smoke and subsequently requiring puffing for liquid reinforcers. Ratner et al. (1974) generated puffing in a cebus monkey in this manner. Jarvik (1967) was able to train fewer than half of his monkeys to suck water through a tube. To improve this percentage, he obtained a group of maternally deprived and semi-isolated monkeys with a high rate of sucking their digits. They puffed cigarettes freely without any other reinforcing consequences; they also puffed on formaldehyde, glacial acetic acid, and isobutyric acid. These early studies relied on observation, lip contact, or water bubbling for response definition; the investigators occasionally observed nasal expulsion of smoke. The monkeys preferred cigarette smoke over hot air, tobacco smoke over tobacco vapor, and very fragrant pipe tobacco over cigarette smoke. No preference was demonstrated between high- and low-nicotine cigarettes, or between cigar and cigarette smoke; one would expect differential control by nicotine if it is the reinforcer maintaining the puffing behavior. In the case of cigar smoking, Armitage et al. (1970) demonstrated that nicotine in cigar smoke is readily absorbed through the oral mucosa, whereas it is not from cigarette smoke, and that this absorption was associated with the high pH of cigar smoke. Jarvik attributed the lack of preference to the duration of the drug effect, which may have made it difficult to discriminate between the consequences of the two smoke sources, assuming that nicotine was maintaining the puffing. Jarvik also demonstrated that water reinforcement could produce tenfold to twentyfold increases in the rate of puffing.

Glick et al. (1970) used lip contact on either of two mouthpieces as a measure of puffing and maintained this performance on a fixed ratio (up to 30 lip contacts per water reward); this baseline was used to evaluate the effects of drug treatment on puffing rates. Mecamylamine, a ganglionic blocking agent, irreversibly eliminated smoke puffing in two animals, had no effect on a third, and produced reduction followed by recovery of the smoke puffing preference in a fourth. The third and fourth animals were then administered varying doses of pentobarbital, hexamethonium, scopolamine, and amphetamine, in that order. Pentobarbital decreased the rate of puffing but did not alter the preference for smoke over air. Hexamethonium, another ganglionic blocking agent, reversed the preference while decreasing rate at large doses. Scopolamine and d-amphetamine reversed the preferences and greatly decreased the fixed ratio puffing rates. The pentobarbital effects indicated that preference reversal was not simply an artifact of rate reduction. A further experiment suggested that the scopolamine and amphetamine effects might be attributable to increased thirst, since water deprivation may increase the aversiveness of tobacco smoke. The hexamethonium and mecamlamine reversals of puffing preferences suggest that the reinforcing properties of cigarette smoke might represent pharmacologic effects other

than olfactory and gustatory effects. A subsequent study (Robinson et al. 1974) utilizing radioactive smoke indicated that some smoke was inhaled into the lungs with this training procedure.

Rucker (1970) maintained cigarette puffing in monkeys with a water reinforcer and examined the effects of fixed ratio size on puff volume, peak flow rate, and puff duration. An appendix to this thesis documents numerous attempts and strategies to produce inhalation. He instituted a progressive puff volume requirement that increased by 10 percent with each puff and decreased by 10 percent after four failures. He then changed the requirement to an increase equal to 10 percent of the amount by which the monkey exceeded the preceding requirement, with no decrement in the requirement. These procedures produced puffs that would not exceed 100 milliseconds in duration; the animals were sucking vigorously. Water deprivation was increased; attempts were made to reinforce blowing and, by manipulating the characteristics of the spout, to make puffing impossible. He differentially reinforced longer puff durations, which rarely exceeded 300 milliseconds and added resistance to the air flow, again without successful production of inhalation, as judged by the volume of the response. The monkeys failed to continue puffing in the absence of liquid reinforcement.

A baboon model of cigarette smoking also has been developed, again by using water as a reinforcer for maintaining a minimum negative pressure and duration on a mouthpiece (McGill et al. 1978). The criterion for smoke inhalation was elevated blood carbon monoxide levels in comparison to a presmoking baseline; CO levels in nonsmoking animals in the smoking room were not reported. Animals obtained their entire water ration in this manner, puffing on up to 48 cigarettes per day at spaced intervals throughout a 12-hour day. One attendant could maintain 20 animals on this regime, making Large chronic studies feasible.

This preparation has been used to examine the effects of nicotine content on puffing performance (Rogers et al. 1985), and to study bronchial reactivity following cigarette (Roehrs et al. 1981) or nicotine aerosol puffing (Wallis et al. 1982). The preparation has also been used for an extensive series of studies on thyroid hormone levels (Sepkovic et al. 1988), on atherosclerosis induction (Rogers et al. 1980, Rogers et al. 1988), on urinary mutagen formation (Marshall et al. 1983), on alveolar macrophage migration (Fine et al. 1981), and on bronchoalveolar lavage fluids (Rogers et al. 1981; Kolb et al. 1981; Radhakrishnamurthy et al. 1983).

Ando and Yanagita (1981) trained 14 rhesus monkeys to suck liquids through a tube; they then maintained air sucking at a tube using sweet fluids as a reinforcer at an adjacent spout. Animals were given prolonged periods of schedule-controlled puffing, where either a progressively increasing puff duration was required to produce liquid, or a tandem fixed-interval fixed-ratio schedule of puffing was in effect; in either circumstance, the

animals were given access to cigarettes in the afternoon without any other consequence for periods that were gradually lengthened to 20 hours. At the time of their report, only 2 of the 14 animals had developed sustained "voluntary smoking" that lasted for 2 or more years; in the face of great variability, the authors reported that low-nicotine cigarettes seemed to lead to decreases in smoking. In two animals that did not sustain voluntary smoking, schedule-controlled smoking was established using a sweet reinforcer, and control of the performance by the schedule of reinforcement was demonstrated. Schedule-controlled smoking was associated with elevated blood levels of nicotine. Yanagita et al. (1983) reported that 10 of the 14 monkeys continued to puff for a month or so after termination of the reinforcement contingency, and that the two chronic voluntary smokers continued to smoke from 1976 through the time of the later report.

Because the success rate was low with these procedures, Ando et al. (1986) tried two other techniques. In the first experiment, with two monkeys, smoking was established with a progressive puff duration requirement; the animals were then shifted to see if smoking could be maintained adjunctively by reinforcing nozzle licking at a separate tube with different values of a random interval schedule. One animal's puffing waned and did not recover; in the other animal, performance was maintained fairly well at short random-interval values. In the second experiment, four other monkeys were shifted from a random-interval smoking contingency with a 0.2 second minimum response duration to a modified Sidman avoidance schedule. When this performance stabilized at a low shock-delivery rate, the avoidance contingency was terminated; under these extinction conditions, two quit within 15 sessions, but the remaining two persisted for 50 and 80 sessions.

CANNABIS (MARIJUANA, DELTA-9-THC, AND HASHISH)

Cole et al. (1971) attempted to study the effects of delta-9-tetrahydrocannabinol (THC) on spaced responding performance by engendering smoking behavior in two chimpanzees and an orangutan. These great apes were reinforced for successively longer puff durations on unlighted cigarettes, the duration ranging from 0.2 to 5.4 seconds. Lights served as feedback for puffing, and M&M's were used as reinforcers. The reinforcer was presented at the time the criterion was exceeded (Pieper and Cole 1973). Criteria were increased between sessions in approximately 250 millisecond increments. When stable, long-duration puffing was established, smoke was gradually introduced into the air stream by reducing the number of holes punched at the base of the lit cigarette. The consistent increases in the rate of the spaced responding performance that occurred immediately following the smoking sessions with THC in the cigarette were consistent with drug intake, but the dose effect functions were equivocal. IV self-administration of delta-9-THC is difficult to engender as evidenced by the heroic but unsuccessful effort of Harris et al. (1974). Pickens et al. (1973) induced IV

delta-9-THC self-administration in animals with a recent history of phencyclidine self-administration.

Pickens and Thompson (1972) reported being able to obtain fixed-ratio schedule control of puffing, maintained by presentation of hashish smoke. Performance was not maintained by heated air. In disagreement with this early report, Pickens et al. (1973) subsequently reported being unable to maintain hashish smoking in the absence of food delivery. Hashish was removed from the burning chamber and the animal was placed on a concurrent (FR3 sucking) (FR5 lever pulling) schedule of food presentation. These values were selected because they produced approximately equal response frequencies in the absence of hashish. When the animal was given hashish for sucking, the frequency of sucking increased (resembling Jarvik's earlier finding with tobacco). An ADA reversal design was executed for two animals. In this design, hashish was available, removed, and made available again, demonstrating a reversal in preference; that is, in the absence of smoke, the animals preferred lever pressing maintained by food. The authors interpreted these findings cautiously, indicating that a decrease in the probability of lever pressing during hashish availability may have been an effect of hashish smoke on lever pressing, rather than a true preference; taste was also a complicating factor.

DIMETHYLTRYPTAMINE

Siegel and Jarvik (1980), using animals with tobacco- and cocaine-puffing histories, established puffing on lettuce cigarettes by requiring a 1-second puff duration for access to 1.5 ml water, the monkeys earned all of their daily water in this manner in a 1-hour session. Termination of the water deprivation eliminated puffing. The subject was then placed in a dark soundproof chamber with free access to food and water; this did not increase lettuce puffing. Animals were then removed from the chamber and puffed on dimethyltryptamine (DMT) cigarettes for access to water; "... after a few puffs on DMT cigarettes, monkeys frequently exhibited aggressive displays, threats, and barks directed at the smoking tube . . ." (Siegel and Jarvik 1980, p. 120). Termination of water deprivation eliminated DMT puffing. Animals were then placed on free access to food and water in the dark chamber, and DMT puffing increased "dramatically"; one animal puffed greatly during the first session, displayed convulsions and spasms, and did not approach the spout again. The other two animals gradually commenced puffing across several days, and clusters of puffs occurred at intervals of about 1 half-hour, approximating DMT's duration of action. Observers recorded increases in behaviors similar to those observed following injection of DMT to animals in darkened environments. Puffing produced some illumination of the chamber under both lettuce and DMT conditions, but was only sustained in the presence of DMT. The authors suggested that "... more complete tests of DMT's reinforcing properties in isolation sessions would require either challenges with forced injections of

DMT or choice trials with cigarettes containing short-acting nonhallucinogenic stimulants . . .” (Siegel and Jarvik 1980, p. 120). Since some puffing occurred spontaneously in the absence of drug or the water reinforcement contingency, DMT puffing may have been due to an agonistic property of the drug on puffing, rather than to a reinforcing property of the drug. If an arbitrary response had been required to produce the opportunity to puff on a lighted cigarette, then a comparison of the frequency of this response with a response with no drug consequence would argue against an agonistic effect of the drug. A subsequent reversal of which arbitrary operant was effective in producing drug access would demonstrate discriminative control of this behavior. A demonstration of control of the frequency of this responding by some parameter of delivered dose would then conclusively demonstrate reinforcing properties of DMT by inhalation. The truism that hallucinogens do not engender self-administration by laboratory animals apparently has arisen because nonarylcylohexylamine hallucinogens have received limited attention, and those that have been studied tend to have delayed onset or prolonged duration of action. Thus, studies of DMT self-administration by either the intravenous or inhalation route would be of interest.

COCAINE

Siegel et al. (1976) prepared lettuce cigarettes with cocaine base. Three monkeys were trained to puff as in the Jarvik (1967) study, and then were permitted for an hour to smoke lettuce or lettuce-cocaine base cigarettes while under water deprivation or not, and were finally given a choice between a lettuce or a lettuce-cocaine base cigarette under conditions of water deprivation. Although the authors did not perform the t-tests of most interest, under nonwater-deprived conditions the monkeys, by any measure, smoked more cocaine than lettuce cigarettes. Whether this performance was induced by a rate-increasing effect of cocaine or by a reinforcing effect of the drug is not known.

Siegel and Jarvik (1980) repeated these observations in a different order, finishing the experiment with nonwater-deprived cocaine smoking; this final condition provided 23-hour access to cocaine cigarettes rather than just 1 hour. Two monkeys tended to distribute puffing fairly evenly across the first few hours and then quit, only to resume after the daily 1-hour break for service. The third animal displayed high rates of puffing that was not associated with increased urinary benzoylecgonine. The authors reported that the rate of puffing did not attenuate across this block of 20 sessions.

THE INFLUENCE OF AEROSOL PHENOMENA ON THE DESIGN OF SUITABLE ANIMAL MODELS

The pattern and efficiency of airway aerosol deposition are dependent on the size of the aerosol and the species exposed (Schlesinger 1985; Schlesinger 1988). We recently characterized the size of crack smoke

(cocaine base aerosol) to be about 2.3 microns with a geometric standard deviation ranging from 1.68 to 2.22 (Snyder et al. 1988). As one would expect from human experience, these particles are small enough to achieve alveolar deposition following oral inhalation. These observations on cocaine particle size have important implications for the development of animal models if comparable patterns of absorption are to be achieved in other species. Large particles impact on surfaces in the upper respiratory tract; because of their high velocity through and the tortuosity of the upper airways of the rodent, even relatively small particles impact in the noses of these species. The rat, for example, is an obligate nose breather, and to achieve penetration to the lung with this species will require the generation of cocaine aerosols with a much smaller particle size.

Smoke, as we think of it in this context, is a condensation aerosol of the drug of interest. As the drug is heated, it vaporizes, only to cool relatively rapidly; as it cools, the vapor condenses spontaneously or upon particles (condensation nuclei) too small to be seen with optical techniques. In the case of drug smoking using a torch and pipe, the torch provides very large numbers of these nuclei. Given a constant airborne drug concentration, the number of nuclei are the predominant determinant of the size of the resultant particles. At the butt of a tobacco cigarette, one might expect 3×10^9 particles per cubic centimeter (Davies 1988). At such high particle numbers, the likelihood of particle collision and subsequent coagulation is great and proceeds very rapidly; Smoluchowski (1917) was the first to assert that the rate of particle coagulation is proportional to the square of the particle count. Thus, particles grow as the smoke ages, and the number of smaller particles decreases by as much as 40 percent in 1 second (Davies 1988).

It should be apparent that substantial technical problems are associated with the rapid generation and delivery of aerosols that are small enough to reach the lungs of small animals at the high air concentrations associated with drug smoking. The higher the desired concentration, the larger the particle tends to be. To decrease the size of the particle, the number of condensation nuclei can be increased; as the number of either condensation nuclei or condensed particles increases, the duration that the particle exists becomes dramatically shorter. Thus, there are practical and engineering limits to what can be achieved. Fortunately, a number of condensation aerosol generators have been designed since the initial LaMer-Sinclair generators of World War II (Muir 1965; Swift 1967). All consist of the same basic design: condensation nuclei flowing through a heated vapor generator into a reheating zone, which assures complete volatilization and subsequent uniform aerosol condensation in a downward flow chimney. Prodi (1972) demonstrated the feasibility of generating solid particles ranging in size from 0.22 to 2.8 microns from materials with melting points in the same range as cocaine base; his innovation provided independent control of vapor concentration and nucleus count. His condensation nucleus generator, however, is not capable of generating high enough counts to maintain these

small particle sizes at high airborne concentrations. Other condensation nucleus generation techniques may be suitable (Swift 1967).

Once such an atmosphere is made., characterizing the material can commence. Most continuous-particle-sizing instruments are designed for monitoring particles in the "clean" rooms of the semiconductor industry, and cannot accommodate the concentrations found at the end of a cigarette or in a burning building. Most such instruments rely on light scattering from single particles and require extraordinarily small measuring volumes and precise optics. Many have small physical paths that cannot accommodate high particle concentrations, bias particle measurement because of sampling artifacts (anisokinetic sampling), or may run at sufficiently high temperatures to alter the particle under measurement. Noncontinuous devices rely on particle impaction and subsequent recovery and quantitation of the impacted material. This process can be complicated by the presence of pyrolysis products; their presence may be difficult to accommodate without the use of sophisticated analytical devices, extensive control calibrations with the pyrolysate, or radioactive materials. The measurement of the air concentration of the chemical of interest poses the same challenge in addition to the special problems associated with trapping particles in contrast to vapors, e.g. cold fingers do not trap particulate materials. Thus, the initial generation and characterization of aerosol test atmospheres requires the scientific ingenuity of a multidisciplinary team; once this effort is under control, the pharmacology and toxicology can commence.

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Research Findings on Smoking of Abused Substances

Research Findings on Smoking of Abused Substances

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