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Oral Nicotine Self-Administration in Rodents

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Abstract

Nicotine addiction is a complex process that begins with self-administration. Consequently, this process has been studied extensively using animal models. A person is usually not called "smoker" if s/he has smoked for a week or a month in a lifetime; in general, a smoker has been smoking for many years. Furthermore, a smoker has free access to cigarettes and can smoke whenever she/he wants, provided there are no social/legal restraints. Subsequently, in an animal model of tobacco addiction, it will be desirable to expose the animal to free access nicotine for 24 hours/day for many weeks, starting at different stages of development.

Keywords

Oral self-administration; Nicotine; Alcohol; Taste; Genetics; Sex differences; Adolescence

Oral nicotine self-administration studies in rodents present some important advantages and mimic human smoking nicely. For example, animals are not food deprived, are exposed to nicotine choice for up to 24 hours a day for extended periods, environmental cues and learning does not interfere with self-administration of nicotine. Oral alcohol self-administration has been used in rodents for over five decades and has contributed significantly to the understanding of alcohol addiction.

We provide a review of literature and compare oral alcohol and nicotine intake in rodents. Methodological issues, post ingestional and systemic effects, discrimination and the important influences of taste, genetic vulnerability, sex and age on intake are discussed. The review ends with recommendations for future research on oral self-administration of nicotine.

Introduction

People smoke tobacco to obtain nicotine. They smoke cigarettes, cigars, and pipes; they chew tobacco, and some inhale tobacco as snuff. In the last decade an increasing number of tobacco users have turned to tobacco substitute products such as the Swedish snus, which deliver nicotine orally in a form that is advertised as being safer than a cigarette. Nicotine from tobacco products is absorbed into the blood through the lungs, and across nasal and buccal mucosa. All of these products activate orosensory pathways, and users often rate satisfaction using terms such as "tastes good". Relatively little is known about those factors

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that influence the taste and palatability of tobacco/nicotine in humans, but researchers using animal models have made progress in this area using oral self-administration procedures. This review will attempt to provide a critical synopsis of the animal model oral nicotine self-administration literature along with recommendations for further research in this area. As suggested by Levin et al. [1] it may be that "consumptive acts are a very important aspect of tobacco addiction and that the consummatory motor acts that are involved in feeding are drafted into the service of drug self-administration in the process of tobacco addiction."

It is readily apparent that people will not initiate tobacco use unless nicotine is present given that we haven't seen widespread use of denicotinized cigarettes. It is true that many researchers have reported that established smokers find denicotinized cigarettes reinforcing, but these reinforcing effects are always less than those of a nicotine-containing cigarette [2–5]. The conclusion that nicotine is absolutely required for the tobacco addiction process presumably explains why tobacco manufacturers go to great lengths to control the nicotine concentration in their products. In some cases, tobacco manufacturers control nicotine concentration by using different blends of tobaccos, but most cigarette manufacturers extract nicotine from tobacco, concentrate the aqueous extract, and spray it back onto a thin tobacco sheet to provide precise and reproducible control of the nicotine concentration in their products [6]. Producing a tobacco product with an optimal nicotine concentration seems to be critically important for producing a product that will be used over, and over, and over again. However, it is also evident that nicotine is not the only factor in tobacco that modulates the addiction process; we have never seen anything that looks like an epidemic of addiction to purified nicotine despite the fact that any amateur chemist could extract and purify nicotine from tobacco.

Tobacco manufacturers seem to be very aware that there is a special relationship between tobacco's sensory factors (taste, aroma) and sales; this issue is discussed, at length, in internal tobacco industry documents [7]. Cigarettes have been described in advertisements as tasting or smelling great. These advertisements may not be nonsense, given that smokers frequently use terms such as "tastes good" when answering questions related to smoker satisfaction [8]. The "tastes good" description for a tobacco product is somewhat curious given that most people describe nicotine's taste as bitter [9, 10], and many describe its effects as burning or irritating [7]. Nicotine elicits responses in chorda tympani neurons that are sensitive to classical bitter tastants such as quinine [11–13]. Findings that indicate the potential importance of taste factors in regulating smoking include: 1) ability to taste phenylthiocarbamide (PTC) seems to affect smoking status (incidence is higher in non-tasters) in Native Americans [14]; 2) female Caucasian PTC non-tasters show more severe signs of dependence than non-tasters [15] and; 3) polymorphisms in two bitter taste receptors (TAS2R16 and TAS2R38) that promote reduced ability to taste bitter substances are positively associated with nicotine dependence in African American women [10]. Added evidence that supports a role for bitter taste receptors in modulating tobacco use comes from the recent finding that the chorda tympani response to nicotine was reduced, but not eliminated, in mice that were engineered to express a null mutation of the gene that produces the bitter taste receptor, TRPM5 [16]. These investigators also concluded that nicotinic cholinergic receptors (nAChRs) modulate the bitter taste via an effect independent of TRPM5 based on the finding that mecamylamine pretreatment further reduced the response to nicotine in the TRPM5 gene knockout mice. These conclusions are consistent with the finding that multiple nAChR subunit mRNAs are found in the same intrapulmonary epithelial cells that express TAS2R38 bitter taste receptors along with several molecules of the bitter taste transduction pathway [9] and with the findings that several cholinergic markers are expressed in the trachea [17] and the auditory tube [18]. These results argue that nicotine's bitter taste arises because it directly activates one, or more, of the bitter taste

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receptors (TAS2R16, TAS2R38, TRPM5), and by activating cells that express nAChRs and other bitter taste receptors (TAS2R38).

It is highly likely that nicotine's effects on sensory pathways play a major role in regulating those factors that make a cigarette taste good. However, the tobacco industry's experiment with potential reduced exposure products (PREPs) suggests that several non-nicotine factors play a major role in modulating tobacco's taste. PREPs are sophisticated nicotine delivery systems that were described by the manufacturers as "safer than standard cigarettes." This assertion was never tested, because cigarette smokers did not switch to these new wave cigarettes, even when they were provided without cost [19, 20]. The principal complaint voiced by those who actually tried the new cigarettes was: "they taste terrible."

The evidence is compelling that, at least at first, people do not like the bitter taste of nicotine and are negatively affected by its irritant properties. We know that smokers, on average, have higher taste thresholds (non-tasters) and that low taste thresholds protect against nicotine dependency. There are ethnic and sex differences, specifically regarding bitter taste [10, 21] and human subjects desensitize to the irritant effects of nicotine [22], but it is not known whether ability to taste nicotine affects tobacco use. American cigarette manufacturers acknowledge that hundreds of compounds are added to tobacco [23]. Some of these compounds enhance nicotine delivery, but additives such as chocolate, cocoa, vanilla and orange extracts, licorice, and menthol are most likely added to tobacco to enhance taste and aroma [24]. Rose [4] argued that non-nicotine components have sensory properties that contribute to the reinforcing effects of tobacco and that are detected in studies that use de-nicotinized cigarettes. This argument is plausible; butit is not clear how these agents might work. Do they, for example, cover up the bitter taste of nicotine or do they have weak reinforcing effects of their own that are enhanced via a learning process that occurs when nicotine and the tastant are paired together many times [25]? Resolving the role(s) that primary (nicotine) and secondary (tastants, etc.) reinforcers play in regulating tobacco addiction may provide critical information that will facilitate better smoking cessation strategies. It may be that animal studies, using oral self-administration procedures, could be used to resolve these issues.

Animal Models of Oral Drug Intake

No one has developed a reliable and convenient method of administering tobacco smoke to animals, but a steadily growing literature describes results of experiments that use the oral route, generally in drinking water, to administer the nicotine (See, for examples, [26–46]). Most of the studies expose rodents to a choice between nicotine-containing solutions and water, and measure oral consumption for durations of 1–4 weeks; in some studies the duration of nicotine exposure is extended. While some studies provide unlimited access to nicotine, others limit exposure to a few hours/day.

Nicotine in the drinking water that is not absorbed immediately in the mouth is absorbed readily in the stomach and intestine and most, but not all, of this nicotine is metabolized in the liver during the first-pass [40, 47]. Therefore, compared to intravenous (i.v.) self-administration in rodents or inhalation in humans, the rate of nicotine entry to the brain is slower and the quantities are lower and more variable.

The methods most frequently used to study oral self-administration of nicotine were pioneered by Peter Rowell and colleagues [48]. Rowell's methods were based on the two-bottle choice methods developed by McClearn and Rodgers [49] to evaluate genetic influences on alcohol intake using inbred mouse strains. With the two-bottle method, animals are singly housed often in their home cage, and are presented with two fluid-filled graduated cylinders or test tubes that are stoppered by a rubber cork-containing sipper tube.

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One of these tubes contains water, or sometimes a saccharin solution (vehicle), and the other contains drug ± saccharin. The tubes are generally inserted through holes in the cage top and consumption from each bottle is measured daily or weekly. The tubes are filled with fresh drug solutions following measurements. Two measures are calculated from the consumption data: 1) preference ratio (volume of drug-containing solution consumed ÷ total volume consumed); and 2) drug dose consumed (volume ÷ concentration of drug solution [mg/ml] ÷ animal weight).

Side preference (drinking the majority of the fluid from one bottle) is a major problem that has plagued oral self-administration studies since their inception. Virtually all of the early studies, and most of the recent ones, have tried to resolve this problem by changing the relative positions of the two bottles every day so that the animal must alter its behavior to find or avoid the drug-containing solution. Other studies counterbalance the position of the bottles containing drug and vehicle solutions across subjects, but keep bottles in the same position for the same animal (e.g. [29, 40]). Recent studies have demonstrated that side preference is largely eliminated if food pellets are placed around both bottles [50] or if the drug and vehicle bottles are placed on the same cage wall an equal distance away from the food hopper [40].

When oral nicotine intake is measured, rats and mice must be individually housed; single housing is an important stress factor (social isolation stress) and may influence the results of oral self-administration studies. Stress may influence responses to nicotine by altering general metabolism and also by changing nicotine-responsive neurotransmitter systems [47, 51–57]. One method that could be used to diminish the confounding effects of single housing is to group house the animals at intervals, especially when the duration of the experiment exceeds 3–4 weeks (see, for example [32]).

Most of the published oral drug self-administration studies have evaluated the intake of single drug concentrations, but this method has limited utility, especially if genetic or sex effects are being measured. Studies that used multiple nicotine concentrations (1–40 mg/l) have been particularly effective in detecting genetic influence on oral nicotine intake [42, 58]. Similarly, alcohol concentrations that range between 1 and 30% (v/v) have been used to measure mouse and rat strain differences in oral alcohol self-administration (reviewed in [59]). For both drugs, preference ratios decrease in a curvilinear fashion as concentration increases and an inverted U concentration-effect curve is often obtained when drug dose is calculated. Strain and sex differences are seen as differences in maximal doses consumed and areas under the concentration vs dose consumed curves. However, some earlier oral drug-reinforcement studies have suggested a relation between increased drug dose and increased intake (Reviewed in [60]).

A principal advantage of free-choice oral self-administration experiments is they are easy to do, but they are not easy to interpret. A major question that confronts those who use oral self-administration techniques in free-choice experiments is: does this procedure measure the reinforcing effects of drugs? This question is complicated by the fact that animals must drink water to survive. The i.v. infusion method is not complicated by the absolute need for water; rats and mice will not die if they don’t get a saline infusion, but the i.v. infusion method does not mimic the way people use tobacco/nicotine. Alcohol researchers have made important progress in answering the “reinforcement question” using a combination of free-choice and operant response experiments. These advances will be described in more detail in a later section, and could be used to test the notion that preference experiments measure the reinforcing effects of nicotine.

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Questions that have been and Should be Addressed

The two-bottle method, along with several slightly modified versions, has been used in hundreds of published studies to address questions that might help us understand those factors that influence alcohol intake in rodents, and possibly, by extension, the biology of alcoholism in humans (see [61, 62] for recent reviews). Studies that have evaluated biological and environmental factors that have focused on nicotine are more limited in comparison. We believe that knowing the alcohol literature can be of value to the nicotine researcher because: 1) It is readily apparent that the two drugs are frequently co-abused by people [63]; and 2) common genes seem to influence alcohol and tobacco abuse in humans [64, 65]. These findings are paralleled by the findings that common genes may influence nicotine and alcohol preference in rats and mice [38, 44, 58, 66] and that rats selectively bred for high alcohol intake also demonstrate high levels of i.v. nicotine infusion [67].

We have chosen to compare nicotine with alcohol byfocusing on a series of questions that have been addressed and answered in the alcohol field. The alcohol findings will be summarized briefly (the reader will find primary references in recent reviews in Crabbe et al. [61, 68, 69]). This summary will be followed bya more detailed description of results, with references, of nicotine studies that have addressed these questions.

Does drug intake vary with the concentration?

Alcohol

In general, preference ratios decrease in a curvilinear fashion with an increase in alcohol concentration, and dose-concentration curves are inverted U in shape. Mouse and rat strains differ in preference ratios, and in the maximal dose consumed (peak value) and area under the curve. Alcohol researchers have concluded that altering alcohol intake as concentration changes reflects an attempt to regulate alcohol intake [68, 69].

Nicotine

The effects of multiple concentrations on nicotine intake have been studied on only a few occasions. Robinson et al. [38, 42] used six inbred strains of mice and showed that all of the mouse strains studied decrease liquid intake from the nicotine bottle when nicotine concentration is increased. Dose vs concentration curves were of the inverted-U type for all strains; the strains differed in maximal dose consumed and the concentration that provided the maximal dose. These findings were confirmed in subsequent studies that used rats [40] and mice [37]. Adult [27, 37] and adolescent [28] mice increased their intake from the nicotine-containing bottle when the concentration of nicotine is reduced. The volume of fluid consumed decreases in both mice [58] and rats [70] when the animals are presented with 4–5 bottles containing water and different concentrations of nicotine.

Are behaviorally effective concentrations of alcohol or nicotine obtained when animals are given a choice between the substance-containing solutions and a water vehicle?

Alcohol

In general, rodents drink both alcohol and water in connection with food [61] and when animals are tested for blood levels around the clock it is apparent that most of the alcohol is consumed during the dark, with the greatest consumption occurring shortly before and after the lights are turned off [71, 72]. A study that compared 12 inbred mouse strains [72] showed that those strains, such as the C57BL/6, with high preference for alcohol readily

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attain blood alcohol levels (ca. 1mg/mL; 20 mM) that resulted in impairments in coordination, as measured by the accelerating rotorod and balance beam tests [71–72].

Nicotine

It is clear that nicotinereadily crosses all biological membranes. It is absorbed rapidly from drinking water and there is no significant blood-brain barrier for nicotine [47, 73–75]. However, it is also readily apparent that a significant first-pass effect limits the amount that can reach the brain when the drug is consumed orally. Rowell et al. [48] demonstrated that mice that were forced to consume nicotine (60 μg/ml) in the drinking water consumed approximately 17.2 mg/kg/day and had steady-state nicotine plasma levels of 34.4 ng/ml. This concentration approximates the plasma [75, 76] and the cerebrospinal [73] nicotine concentrations found in dependent smokers. Rowell suggested that less than 10% of the total nicotine dose was absorbed intact from drinking water. Le Houzec et al. [77] also demonstrated that some nicotine escapes the first-pass metabolism in the liver in a study that found that comparable plasma levels of nicotine were obtained following intragastric injection and free-choice consumption of 0.31 mM nicotine. Adriani et al. [27] also drew the conclusion that first pass metabolism is an important factor that influences the bioavailability of nicotine from a study that measuredplasma cotinine levels in adolescent (early, middle and late) mice that had been given a bottle containing 10 mg/l nicotine 1 h/ day for three days, following water deprivation. Average nicotine intake varied between 1.68 and 1.23 mg/ kg and decreased with increased age. Plasma cotinine levels were 20–40 ng/ml, decreased over time and did not vary with age suggesting higher metabolism in younger mice. These cotinine levels were about 1/3 of expected levels following 1 mg/kg intraperitoneal (i.p.) administration in mice, and comparable to levels in human smokers (15–40 ng/ml).

None of the studies that have determined whether oral nicotine produces pharmacologically relevant concentrations of nicotine in the blood have directly addressed the question: do these concentrations elicit behavioral and/or physiological effects? Addressing this question is especially important because it is likely that the affinities of rodent brain nicotinic receptors are not identical to the affinities of the human receptors; compare the results obtained by Marks et al. [78] using mouse α4β2-type nAChRs with results published by Buisson et al. [79] who studied human α4β2-type nAChRs. While no study has addressed this question directly, several have yielded indirect evidence that suggests that behaviorally effective concentrations of nicotine are achieved by animals placed in a choice situation. An example of this indirect evidence is found in the study done by Glatt et al. [33] that evaluated the nicotine preference of three inbred mouse strains in a standard two-bottle preference test and in a brief access (1 hr) test. Glatt et al. found strain differences in the standard 2-bottle choice test, but not in the limited access test. They argued that the standard test maximizes post-ingestive effects of nicotine whereas the limited access test maximizes orosensory response and minimizes post-ingestive effects. Further, and arguably better, evidence that supports the notion that post-ingestive effects of nicotine intake influence oral intake comes from the finding that pretreatment with nicotinic and dopaminergic (D4) receptor blockers results in a decrease in oral nicotine intake in rats [35]. The finding that the weight gain of rats that had been treated with oral nicotine (two-bottle, free choice) is significantly less than the weight gain seen in control rats provides further support for the assertion that orally-supplied nicotine exerts a systemic effect [40]. The best evidence comes from two elegant studies from the Glick laboratory [80, 81] that established that rats will press a lever for an oral nicotine reward, and that this behavior is altered by pretreatment with the nicotinic receptor antagonist, mecamylamine, and by 18-methoxycordan, an agent that blocks nicotine-induced dopamine release in the nucleus accumbens. These are complemented by genetic studies that used the mouse that demonstrated that strain

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differences in sensitivity to stimulant effects produced by injection with nicotine are significantly correlated with strain differences in oral nicotine intake [38, 42, 58, 82].

Unfortunately, all of these studies provide indirect evidence that support the assertion that oral intake produces nicotine concentrations in the blood and brain that produce behavioral effects. Studies that evaluate behavioral effects of nicotine as the animals are drinking nicotine-containing fluids must be done to provide direct evidence that relates to this question. If such studies are attempted, researchers must study actions of nicotine that are elicited by concentrations of nicotine that are produced by free-choice consumption.

Do genetic factors influence oral alcohol or nicotine intake?

Alcohol

It is absolutely clear that genetic factors influence alcohol intake in both mice and rats. Hundreds of published studies have demonstrated that inbred mouse and rat strains differ in oral alcohol intake, but the most compelling evidence that supports a genetic explanation comes from the reports that multiple mouse and rat lines have been selectively bred for differences in 2-bottle choice for alcohol (reviewed in [61, 83]). The inbred mouse genetic studies have been very reliable given that the correlations of strain mean preference ratios exceeded r = 0.9 for any pair wise correlation of data sets published in over 20 studies [84]. In recent years, quantitative trait locus methods have determined that alcohol intake is regulated in mice by many genes and that no gene explains more than 1–2% of the variance [61].

Nicotine

When compared with alcohol, relatively little is known about genetic regulation of oral nicotine intake. Studies done with inbred mouse strains clearly demonstrate that genetic factors regulate the dramatic strain differences in nicotine intake that have been detected in choice experiments [42, 66]. Inbred strain differences are most often due to genetic actions, but more sophisticated approaches must be used to provide unambiguous evidence that supports a genetic postulate. One of these approaches is quantitative trait locus (QTL) mapping. Li et al. [38] used the QTL method to identify four loci that contain a gene(s) that modulate nicotine preference; this study used F2 hybrid mice derived from high-preferring C57BL/6 and low-preferring C3H mice.

Two studies that used F2 mice derived from C57BL/6 (high-preferring) and low-preferring strains tested the postulate that specific genes modulate nicotine intake. One of these candidate gene studies [85] used C57BL/6- St/bJ crosses to demonstrate that the enzyme that metabolizes nicotine (CYP2A5) influences oral nicotine. This study found that slow metabolizers drank less nicotine, which is consistent with the findings that the incidence of smoking is less in people with slow nicotine metabolism, and slow metabolizers, if they smoke, smoke less [86].

The second candidate gene study [58] demonstrated that a polymorphism in the mouse chrna4 gene influences nicotine preference. The Chrna4 gene codes for the mouse α4 nAChR subunit. This study used a combination of SNP (single nucleotide polymorphism) analysis and gene knockout mice by using F2 hybrids derived from nicotinic receptor subunit β2 null mutant mice where the mutant gene had been bred onto a high- preferring C57BL/6 background. The low-preferring A/J strain was used as the other parental strain for the F2 hybrids. The β2 null mutant mice were used in this study because they do not express any α4β2-containing nAChRs. Thus, these mice do not expressα4β2, α4β2β3 and α4α5β2 nAChRs in any brain region. An association between the Chrna4 A529T polymorphism and oral nicotine intake was seen in F2 mice that actually express α4β2* nicotinic receptors, but

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no association was seen between oral nicotine preference and the Chrna4 A529T polymorphism in those F2 mice that do not express α4β2* nicotinic cholinergic receptors. This result provides unequivocal evidence that the A529T Chrna4 polymorphism causes alterations in nicotine preference. Parenthetically, Li et al. [38] did not detect a QTL on chromosome 2 where Chrna4 is expressed. This finding supports the conclusions drawn by Butt et al. [58] because the C57BL/6 and C3H mice express the 529T variant of the Chrna4 A529T polymorphism. The finding that a polymorphism in the gene that encodes for the α4 subunit affects oral nicotine intake parallels the finding, made many times in many studies (see [64] for a review), that polymorphisms in the human α5 nAChR subunit gene (CHRNA5)) seem to affect human tobacco and alcohol intake.. Thus, mouse genetic studies point towards a role for α4-containing AChRs, and human genetic studies indicate that the α4α5β2 nAChRs are the most important members of the α4 family. It may be that MAO-A also plays an important role in regulating nicotine intake because the nicotine intake of MAO-A null mutant mice is slightly less than that of wild-type controls [87]. Taken together, the mouse studies indicate that oral nicotine intake is a complex trait that is modulated by multiple genes, and some of these genes may have been identified.

The possibility thatgenetic factors also regulate nicotine intake in the rat has also been studied, although the methods used to assess this question are less sophisticated than those used in the mouse. Todte et al. [44] have published the only study that attempted to compare directly the oral nicotine intake of two rat strains (Brown Norway [BNR] and Wistar Kyoto [WKR]) using a two-bottle choice method. The preferences of these strains for nicotine, alcohol, cocaine, and morphine were evaluated in this study. The study used limited concentrations of all of the drugs, which limits interpretation. Nonetheless, the finding that WKR rats consumed more nicotine than the BNR suggests that genetic factors influence oral nicotine intake. Less convincing support for the assertion that genetic factors influence oral nicotine intake comes from studies that used only one rat strain [29, 31, 41, 45]. However, when these studies are compared it is readily evident that the strains differ in oral nicotine intake.

Todte et al. [44] also reported that WKR rats consumed more alcohol than the BNR rats; the strains did not differ for cocaine and morphine. Similar strain differences might mean that the same genes, or more likely subset of genes, influence oral nicotine and alcohol intake. This postulate cannot be accepted readily given that only two rat strains have been compared, but, should be considered given that the strain rank order for nicotine and alcohol consumption using six inbred mouse strains is identical [58]. The finding that the WKR and BNR strains did not differ in oral cocaine and morphine preference [44] may mean that different sets of genes influence the oral intake of nicotine/alcohol vs cocaine and morphine.

When oral nicotine intake is studied in outbred rat strains, tremendous variance is seen [30, 39, 40]. Nesil et al. [40] found that the Sprague-Dawley rats used in their studies could be divided into nicotine preferring and non-preferring subpopulations using the Ward cluster analyses. Similarly, Maehler et al. [39] showed that adolescent or adult, male or female rats could always be divided into three subgroups based on their nicotine preference and intake. Both the Maehler et al. [39] and Nesil et al. [40] studies found that minimum and maximum nicotine preferring rats have a consistent pattern of intake, but those in the median group show marked variability. Galli and Wolffgramm [32] also did a test-retest experiment but in the retest experiment quinine was added to the nicotine solution in an attempt to make its taste aversive. Those rats with intermediate levels of preference decreased their nicotine intake when quinine was added, but those rats with high nicotine intake continued to consume high doses of nicotine despite the bitter taste of quinine. These studies indicate that nicotine intake in inbred and out bred rats is influenced by genetic factors, but a genetic

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selection study, starting with an out bred rat strain, or an F2 hybrid derived from inbred strains, is needed to provide an unequivocal test for a genetic hypothesis.

Is oral alcohol or nicotine intake influenced by taste factors?

Alcohol

The evidence that taste factors play a major role in modulating oral alcohol intake in rodents is very convincing. The animal studies were based on the finding that preference for sweet taste seems to be a very important factor that serves to increase vulnerability to alcohol abuse in humans [88]. A convincing literature indicates that common genetic factors influence sensitivity to sweet taste and oral alcohol intake in inbred mouse strains [89] and congenic strains [90]. Rat stains selectively bred for alcohol preference also show higher preference for sucrose and saccharin when compared to controls [91, 92]. These findings, coupled with the finding that many mouse strains show an increase in alcohol intake (dose) and preference ratios when saccharin is added to both drinking fluids in a 2-bottle choice [50], provides compelling data that support the assertion that sweet taste factors play an important role in regulating oral alcohol intake.

Green and Grahame [62] concluded in their review of the relevant literature that both reinforcing effects of alcohol and taste factors are being measured with the two-bottle choice test. They drew the conclusion that reinforcement is being measured based on their finding that mouse and rat strain oral self-administration (preference ratio and maximum dose) is highly and positively correlated with levels of operant oral self-administration (rat/mouse presses a lever to obtain an oral alcohol reward). However, they noted that taste factors play a dominant role in some strains. For example, the DBA strain totally avoids alcohol, but DBA mice are one of only a very few mouse strains that will self-administer alcohol intravenously [93]. Thus, it seems that alcohol is reinforcing for DBA mice, but taste factors overwhelm this effect when the drug is made available orally.

Nicotine

The literature that indicates that taste plays an important role in modulating oral nicotine intake in rodent models is not very well developed. Indeed, no conclusion can be drawn based on the currently available literature. Genetic factors influence taste perception in rodents (see [94] for a recent review), and inbred mouse strains show substantial variation in the intake of bitter substances (see, for examples: [33, 95–97]). The observation that the rank order of strains tested for bitter taste preference using a two-bottle choice strategy is similar to the rank order of the same strains for nicotine intake [42] suggests that strain differences in nicotine intake may reflect strain differences in bitter taste perception or response. However, Robinson et al. [42] concluded that the bitter taste of nicotine did not influence strain differences in [−]-nicotine intake based on their finding that strain distribution patterns for the oral intake of the biologically active form of nicotine ([−]-nicotine) were different from the patterns obtained when [+]-nicotine was tested. This conclusion was based on the supposition that the bitter taste of the two isomers of nicotine is similar, and that the tongue does not have nAChRs that modulate the taste of nicotine. Given that more recent studies have found that nAChRs are expressed in mucosal taste cells [9] this conclusion must be accepted with caution. Robinson et al. [42] also reported that the addition of saccharin to both test solutions did not alter preference ratios or dose consumed in five of the six strains that were tested. This finding also supports the “no effect” conclusion, but must also be viewed with caution because only one saccharin concentration was tested. Glatt et al. [33] also concluded that taste factors did not influence strain differences in oral nicotine intake in their study that compared three inbred mouse strains for nicotine intake in limited access and prolonged exposure tests. However, this conclusion must also be accepted with caution

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because three strains does not provide adequate statistical power and because it is not absolutely clear that the limited access and 2-weeks, 2-bottle choice tests actually discriminate taste effects from post-ingestive effects. Thus, studies done using genetic strategies in the mouse have yielded data that are conflicting; it is not clear whether taste factors are influencing oral nicotine intake in the mouse.

Several studies have attempted to determine whether masking the bitter taste of nicotine with a sweetener will increase nicotine intake. As mentioned previously, five of six mouse strains tested by Robinson et al. [42] did not change their nicotine intake when saccharin was added to the test solutions. This finding differs dramatically from the findings reported by Smith et al. [43] who exposed adult male Wistar rats to an unlimited choice of nicotine and water, with or without sucrose added. Addition of sucrose increased nicotine consumption and sucrose + nicotine solutions were more reinforcing than sucrose solutions alone. Nesil et al. [40] reported similar findings when saccharin was added to mask the bitter taste of nicotine when male Sprague-Dawley rats were tested. However, no effect of saccharin was seen when females were tested. Taken together, the mouse and rat data suggest that adding something with a sweet taste may increase nicotine intake, but the effect may be readily apparent only in rats and a limited number of mouse strains. Moreover, the effect in rats may be limited to males.

Does the oral free-choice experiment measure the reinforcing effects of alcohol and nicotine?

Alcohol

This question may be the most important one to address given that most researchers have used the oral self-administration procedure to study what may be the most important component of the addiction process. This question of whether free-choice experiments measure the reinforcing effects of alcohol was debated for decades by alcohol researchers, but remained unresolved until experiments were done using operant procedures. Green and Grahame [62] concluded in their review of the relevant literature that both reinforcing effects of alcohol are being measured with the two-bottle choice test. They drew this conclusion based on their finding that mouse and rat strain oral self-administration (preference ratio and maximum dose) is highly and positively correlated with levels of operant oral self-administration (rat/mouse presses a lever to obtain an oral alcohol reward).

Nicotine

It seems that rats will perform an operant response to obtain an oral dose of nicotine [80, 81] and rats will self-administer more nicotine if they are presented with a drop of water immediately after the operant response (i.e. responding is rewarded by i.v. nicotine and oral water) [1]. These findings, if pursued, would allow nicotine researchers to use techniques such as strain comparisons to test the hypothesis that free-choice nicotine consumption measures the reinforcing effects of nicotine. If nicotine preferring strains will also work for an oral dose of nicotine, and low-preferring strains do not, we may be able to draw the conclusion, with confidence, that the nicotine free-choice experiment measures the reinforcing effects of nicotine.

Is the behavior stable?

Alcohol

Many studies have evaluated oral alcohol intake in both mice and rats for prolonged periods [68, 69]. In general, strain and sex differences seem to be stable. Effects of age (adolescence vs adults) are evident.

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Nicotine

Flynn et al. [31] found that adult male Sprague-Dawley rats increase their nicotine intaketo the point that they develop a preference for the nicotine solution suggesting enhanced palatability following pairings with the positive post-oral reinforcement of nicotine.. More recently, Nesil et al. [40] found that Sprague-Dawley rats (both sexes) decrease their oral nicotine intake with prolonged testing starting at adolescence and continued for 23 weeks through adulthood. It is not clear if long-term treatment has similar effects in the mouse because most of the mouse studies used short-term assays or changed nicotine concentrations in longer-term studies. Nonetheless, the rat studies suggest that the behavior changes with nicotine exposure. It is not clear whether changes in the reinforcing effects of nicotine (tolerance or sensitization) occur or whether changes in taste factors are responsible for these changes, but it may be that short-term studies will yield results that are applicable to smoking initiation whereas longer term studies may be required to understand the addiction process.

Does sex influence oral alcohol or nicotine intake?

Alcohol

This question has been addressed in countless studies and has been uniformly answered in the affirmative; see Yoneyama et al. [50] and Phillips et al. [98] for recently published studies using the mouse and Le et al. [99] and Vetter-O'Hagen and colleagues [100–102] for studies that compared the sexes in the rat. In both mice and rats, females consume more than males on a g/kg basis.

Nicotine

Some of the changes induced by nicotine are sexually dimorphic and most require chronic exposure (reviewed by [103, 104]). When adolescent male and female rats received nicotine through implanted mini pumps [104] or male and female mice were exposed to the two-bottle free choice nicotine condition [36], females consumed more nicotine than males but the serum cotinine levels were similar, suggesting sex differences in nicotine metabolism and related pharmacokinetic processes. Nicotine self-administration, using the i.v. route with an operant paradigm, is reported to be higher in adolescent female Sprague Dawley rats than in adults [105], and this difference persists into adulthood. Although similar findings are reported in male rats as well, the difference does not persist into adulthood and the amount of nicotine male rats self- administer gradually declines [106]. Most of the studies involving sex differences used adolescent animals; these studies will be summarized in the following sections.

Do adolescent and adult rodents consume different amounts of nicotine?

Adolescence is a chaotic period in development, not only from a psychological standpoint, but also and more importantly, regarding brain plasticity. During adolescence, the interaction of nicotine with biological processes results in long-lasting effects in brain structure, function and vulnerability to various disorders including addiction. In humans, the first encounter with nicotine usually is at this stage. In animal models of addiction, most of the abused substances have been shown to have different effects during adolescence and adulthood. Furthermore these differences are substance-specific, and can be contrasting in some cases. For example some neurobehavioral responses to alcohol or nicotine in adolescent and adult rats are dissimilar [107]. There are studies showing that both male and female adolescent mice [36] and rats [40] consume more nicotine (2-bottle, free choice, oral) than adults, that female adolescent Sprague-Dawley rats self-administer significantly higher doses of nicotine intravenously compared to adults [105], and that the rewarding effects of

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nicotine in the conditioned place preference test is greater in adolescent than adult male [108] and female [109] mice.

Studies on adolescent tobacco use have indicated that susceptibility to dependence varies between individuals, and while some people become addicted shortly after the first exposure to tobacco products, others do not [110]. However, the first symptom of dependence usually predicts continued use and loss of control, and girls are reported to develop symptoms faster than boys. In studies with human subjects, adolescents usually do not serve as their own control, but oral self-administration studies in rodents provide an opportunity to monitor the nicotine intake of animals that were exposed to nicotine from adolescence through adulthood and compare the change in consumption patterns using within-subjects analyses. Nesil et al. [40] exposed rats to a free choice of oral nicotine self-administration from five to 28 weeks of age and compared intake with another group that received nicotine only as adults; the results show that adolescent-onset rats consume less nicotine than adult-onset animals. Shram et al. [111] studied nicotine self-administration under different reinforcement schedules; followed by tests for extinction and reinstatement of nicotine seeking in adolescent and adult male rats. Rats exposed to nicotine as adults displayed greater resistance to extinction of nicotine taking behavior compared to rats exposed to nicotine as adolescents. Reinstatement, on the other hand, was independent of the age first exposure. Subsequently, the authors propose that nicotine is less reinforcing in adolescent compared with adult rats and therefore the greater susceptibility to smoking during adolescence may be related to factors other than the reinforcing effects of nicotine in humans [111].

On the other hand, nicotine self-administration, using the i.v. route with an operant paradigm, is reported to be higher in adolescent female Sprague Dawley rats than in adults [105], and this difference persisted into adulthood. Although similar findings are reported in male rats as well, the difference did not persist into adulthood and the amount of nicotine male rats self-administered gradually declined [106]. Marshall et al. [112], using adolescent and adult Sprague Dawley male and female rats, found that nicotine consumption was higher in adolescents than adults, furthermore, individual differences in nicotine consumption were noted. In the studies using the operant paradigm, the possible effect of differences in learning between adolescent and adult rats was mentioned as a possible factor, which would contribute to the difference in nicotine self-administration. Unlike i.v. self-administration studies, learning is not an important factor in oral nicotine self-administration; therefore the higher nicotine consumption of adolescent rats than adults cannot be explained by differences learning performance.

The apparent contrast between the rodent studies and epidemiological literature regarding adult vulnerability to tobacco addiction following adolescent exposure could be explained by psychosocial and environmental influences, notwithstanding the possible contribution of tobacco constituents other than nicotine. Along these lines, it should also be considered that while all the adolescent rats have equal opportunity to access to nicotine easily, human adolescents usually have serious constraints including factors such as pressure from parents, cost of cigarettes and the restricted sales. Therefore adolescent smokers, unlike laboratory rodents, may be representative of an initially vulnerable population. Furthermore, rodent studies performed by Slotkin [104] demonstrate that nicotine exposure during adolescence produces cell damage and impairs the programming of synaptic activity, which would impact adult vulnerability substantially.

Another interesting finding of the Nesil et al. [40] study was the change in the pattern of nicotine consumption as rats progress from adolescence to adulthood, in other words, the stability of behavior. Female rats, especially those with minimum preference for nicotine,

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are reported to be the most persistent group in their preference pattern; more than 85% of the female rats that were designated as minimum consumers as adolescents were still minimum consumers after 23 weeks of testing.

Summary and Recommendations

It is clear that both rats and mice will drink nicotine-containing solutions, and that animals adjust dose by changing intake with changes in nicotine concentration. It is also apparent that strain differences (genetic factors), sex, and age influence this behavior. It is also likely that behaviorally relevant concentrations of nicotine get to the brain of those animals (strains) that have high preference for nicotine. These results are very similar to results that have been obtained in alcohol studies. However, potential differences between alcohol and nicotine have been observed. Most notably, a sufficient number of studies have clearly shown that alcohol can be rewarding when given orally; rats and mice will press a lever for an oral alcohol reward. Alcohol researchers concluded that the reinforcing effects of alcohol are measured in choice experiments based on results obtained using more than one strain: operant self-administration of alcohol and 2-bottle choice is highly correlated across multiple mouse and rat strains. Rats [80, 81] will work for an oral nicotine reward, but no one has done studies in multiple strains, and no mouse studies have been done (in any strain). Consequently, a test that has provided a powerful test of the “Free-choice experiments measure reinforcing actions of a drug” has not been done for nicotine. We recommend, strongly, that nicotine researchers compare operant self-administration of nicotine with free-choice selection of nicotine in multiple rat/mouse strains.

The literature clearly supports the argument that taste, particularly sweet taste, modulates oral alcohol intake in rodents: mouse and rat strain variability in preference for sweet tastants (sucrose, saccharin) is significantly correlated with variability in preference for alcohol, and adding sweeteners to alcohol-containing solutions consistently increases alcohol intake in both species. Clear, consistent effects of sweet taste on nicotine intake have not been detected, but we believe that most of the studies done, to date, were not adequately designed to evaluate the taste question. A major problem with all of the sweet-taste and nicotine studies is only one sweetener concentration was used in most studies. Moreover, the taste studies done, to date, have largely ignored the fact that nicotine has a bitter taste. It seems possible that studies that examine the interaction between bitter taste and nicotine intake might provide data that are more relevant to the human condition. We strongly recommend that future studies modify the method in a way that would allow measurement of the effects of tobacco additives on oral nicotine intake.

Unlike i.v. self-administration, the oral nicotine self-administration method has high construct validity for human tobacco use (the animal model resembles the human model). However, many questions must be addressed before the method can be used routinely. We believe that determining whether the method measures the reinforcing effects of nicotine, and whether taste factors modulate nicotine intake are among the most important of the many questions that should be investigated. Attacking the many questions may be daunting, but a payoff should come when the method helps us answer questions concerning the reinforcing effects of nicotine that have not been addressed adequately using the i.v. self-administration approach.

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