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Solution concentration influences voluntary consumption of nicotine under multiple bottle conditions

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ABSTRACT

Female Sprague Dawley rats were given a choice between two concentrations of nicotine solution (5 μg/ml and 8 μg/ml) and water in a 5-bottle arrangement for 25 days. Rats developed clear bottle discrimination, drinking more of the 5 μg/ml nicotine solution than water or the higher concentration nicotine solution. Further, intake patterns were sensitive to exposure. Differences in consumption of the three solutions (5 μg/ml vs. 8 μg/ml vs. water) were minimal during initial exposure days but became clear and stable with chronic exposure. Control rats given 5 bottles of water drank equally from all bottles and showed no development of preference for bottle position. Results suggest that both environmental availability and post-ingestional effects of nicotine contribute to the voluntarily oral consumption of nicotine solutions by rats. The influence of these two factors, however, is modulated by exposure. Availability appears to drive consumption initially, but the impact of concentration exerts more control over consumption with continued exposure. These data support the utility of oral methods of nicotine self-administration in the laboratory rat and suggest the need for further investigations into the biological impact of nicotine consumed orally.

1. Introduction

The two-bottle free-choice method is commonly used as a means of assessing the voluntary intake of ethanol and other solutions by laboratory rats and mice (Bachmanov et al., 2002; Bachmanov et al., 1996a,b). It has also been adapted for testing drugs of abuse such as cocaine, morphine and nicotine (Adriani et al., 2002; Dadmarz and Vogel, 2003; Maehler et al., 2000; Smith and Roberts, 1995) that are typically administered via more direct and invasive routes. Drug intake, assessed with the oral free-choice method, is assumed to reflect "voluntary" behavior as animals are free to choose between water and the drug solution (Bachmanov et al., 2002; Bachmanov et al., 1996b; Tordoff and Bachmanov, 2003). Further, the simplicity of preparation and non-invasive nature of exposure associated with oral procedures, allows for examination of preference as well as intake patterns across prolonged exposure periods. Thus, this method is suitable for answering questions about initial vs. chronic drug exposure, the impact of exposure across developmental periods, and the interaction of voluntary exposure with other behaviors.

Investigations of voluntary nicotine self administration using the two-bottle free choice method have demonstrated that laboratory rats generally fail to show preference for nicotine solutions over water (Flynn et al., 1989). In fact some data indicate lower than chance levels of intake in rats when nicotine concentrations reach or exceed 5 μg/ml (Flynn et al., 1989); a finding assumed to reflect that rats are avoiding the bitter taste of nicotine dissolved in water. Although manipulations such as sweetening nicotine solutions (Smith and Roberts, 1995) and depriving animals of food or water (Glick et al., 1996; Lang et al., 1997) have been fruitful in augmenting levels of nicotine ingested, they provide little insight into the factors controlling voluntary consumption of nicotine. Interestingly, mice show no such avoidance of nicotine solutions and they have been used in numerous studies to elucidate factors that contribute to voluntary nicotine self administration as well as the impact of nicotine administered orally (Adriani et al., 2004; Klein et al., 2004; Siu et al., 2006).

Mounting evidence indicates that rats will self-administer nicotine when delivered via direct infusions into the bloodstream (DeNoble and Mele, 2006; Levin et al., 2006, 2007; O'Dell et al., 2007; O'Dell and Koob, 2007; Shram et al., 2008; Valentine et al., 1997). Thus, with rats at least, the issue of nicotine delivery route is an important one. Given recent evidence that developmental factors such as adolescent exposure may alter sensitivity to nicotine in rats (Adriani et al., 2006; Belluzzi et al., 2004; Cheeta et al., 2001; Chen et al., 2007; Levin et al., 2003, 2007) our goal was to determine if the oral method which is well suited for investigations involving prolonged exposure and growing animals, is a viable experimental approach to modeling voluntary nicotine self-administration in the rat.

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Two lines of evidence presented recently contribute to the position that the oral method should not be abandoned as a valid model of nicotine self-administration in rats. In the first case, using the two-bottle procedure Dadmarz and Vogel (2003) demonstrated striking individual differences in the amount of nicotine that outbred N:NIH rats voluntarily consumed. Although intake levels varied greatly between rats, individual rats were consistent in the amount of nicotine they consumed falling clearly into categories of low and high consumers. They argue that nicotine self-administration by rats depends on individual reactions to nicotine, rather than simply on the provision of nicotine. The finding of individual differences in the sensitivity of rats to nicotine is in line with evidence indicating that humans exhibit markedly different reactions to nicotine, the use of tobacco products, and nicotine dependence (DiFranza et al., 2007; Donny et al., 2008; Perkins, 1995; Pomerleau et al., 1993, 2005; Shiffman, 1991; Shiffman and Sayette, 2005). Thus, the data of Dadmarz and Vogel (2003) accurately reflect an important relationship between individual factors and possible pharmacological reactions to nicotine consumed orally by rats.

In the second case, our laboratory recently demonstrated that the amount of nicotine solution consumed by female Sprague Dawley rats was in large part dependent upon the number of bottles containing the solution available in the home cage (Biondolillo and Pearce, 2007). The multiple bottle effect, which has been well established with ethanol (Tordoff and Bachmanov, 2003) and other macronutrients (Bachmanov et al., 1996a) also holds for rats consuming oral nicotine under voluntary conditions, at least at the concentration tested (3 μg/ml). Increasing the ratio of bottles containing nicotine solution to those containing water directly influenced the amount of nicotine solution (or inversely water) that rats consumed. Environmental availability, like individual reactions to nicotine, has been established as a critical factor involved in the initiation of tobacco use by humans (Christophi et al., 2008; Pokorny et al., 2003). Given that consumption of oral nicotine by rats is both sensitive to individual differences and environmental availability, and given the recent interest in developmental factors associated with nicotine sensitivity, we suggest that oral methods may be a suitable approach to addressing such questions.

The goal of the study reported here was to replicate earlier findings and to extend our understanding of the multiple bottle effect as it relates to nicotine solutions. Although the effect is clear and the method provides an easy means of increasing levels of voluntary nicotine consumption, a complete understanding of the effect is lacking. The most parsimonious explanation has already been presented as a simple reaction to environmental availability having perhaps little or nothing to do with the pharmacological impact (Tordoff and Bachmanov, 2003) of, in this case, nicotine. The study reported here was designed to examine the impact of nicotine solution concentration and availability on both initial and chronic voluntary consumption in rats using the multiple bottle procedure.

As in earlier work (Biondolillo and Pearce, 2007), rats were presented with 4 bottles of nicotine solution and 1 bottle of water. In the present study, two of the four bottles contained a 5 μg/ml nicotine solution and the other two bottles contained an 8 μg/ml nicotine solution. This is in contrast to all nicotine bottles containing the same concentration (3 μg/ml). We hoped to test the influence of availability by increasing nicotine concentration to one that rats have been shown to consume, but which supports lower levels of voluntary consumption than water. It was hypothesized that if nicotine consumption is controlled primarily by availability then intake would be comparable for both nicotine solutions. This manipulation would thus provide an easy means of increasing levels of nicotine voluntarily ingested by rats. It would also indicate that environmental availability is a dominant factor in oral nicotine self-administration. If, on the other hand, rats discriminated between solutions, tracking the immediacy with which the discrimination emerged would provide an indication of whether the discrimination was based on immediate oral effects or on delayed post-ingestional effects of solutions. Although the influence of nicotine concentration on intake has been examined (Dadmarz and Vogel, 2003), it has only been considered under conditions of consecutive availability. This is the first study of which we are aware, in which rats were given the ongoing choice between water and two concentrations of nicotine solution.

2. Materials and methods

2.1. Subjects

Sixteen experimentally naïve female Sprague Dawley rats (Harlan Laboratory, Indianapolis, IN), 55–58 days old at the beginning of the study, served as subjects. They were housed in a common colony room, maintained at 20–22 °C in clear polycarbonate cages (Allentown Caging) fitted with stainless steel wire lids. Cages were filled with Cell-Sorb Plus bedding material which was changed every 3 days or sooner if needed. The colony room was on a 12:12 light:dark cycle with lights on at 0500. Rats were housed in pairs for a 5 day acclimation period and then separated into individual cages for the duration of the experiment. All rats had free access to water and a Nylabone chew (BioServ) except during 40 minute operant sessions which took place at the same time Monday–Friday for the duration of the study. Operant lever presses were reinforced with 4 mg food pellets (BioServ) according to a VI 30 s schedule of reinforcement. No training procedures were used to establish the lever press response and rats were under minimal food deprivation receiving a daily ration of 25–35 g of standard laboratory Rat Chow (Purina 5012). Individual rations were established and adjusted by determining the amount of food consumed without restraint during the 21 hour period following an operant session. All rats consumed daily amounts well within standard daily intake levels for free feeding animals. The operant data are being treated as pilot data and are not presented in this report. All procedures used in the study reported here were approved by the University IACUC.

2.2. Experimental design and procedures

Rats were randomly assigned to one of 2 drinking conditions; water only (W/W) or nicotine/water choice (N/W). Rats in both drinking conditions had access to 5 bottles arranged across the top of the home cage with drinking spouts inserted through the wire cage lid. Rats in group W/W had water in all 5 bottles; rats in group N/W had one bottle of water, placed in the middle (third) position and 2 bottles of nicotine solution to the left (first and second position) and right (fourth and fifth position) of the water bottle.

Two nicotine solutions were made by mixing nicotine base (Sigma Aldrich) in tap water at concentrations of 5 μg/ml and 8 μg/ml nicotine base/water. Results from previous studies indicate rats tend to consume relatively small amounts of nicotine in concentrations exceeding 1 μg/ml (Flynn et al., 1989). Nicotine solutions were mixed as needed, approximately once a week, and stored in amber bottles until distributed to subjects daily. Nicotine base remained refrigerated. All rats in condition N/W received nicotine solutions in the order 5, 8, W, 5, 8. This arrangement guaranteed that each nicotine solution was in a distal and medial position relative to water; thereby increasing the chance rats would initially sample at least some of all solutions. Previous work in our laboratory with the 5-bottle free-choice procedure has consistently demonstrated that although initial bottle preferences may exist for individuals, rats consume at least some liquid from all 5 bottles especially during early days of exposure. Bottle positions remained constant throughout the study to increase the likelihood that rats could discriminate solutions, and their effects, based on bottle position. Bottles were filled with nicotine solution or water daily, weighed, and placed on top of home cages. Approximately 23.5 h later bottles were removed, weighed again and a difference score was calculated by subtracting removal bottle weight from placement weight (g). This score was used to reflect intake from individual bottles in

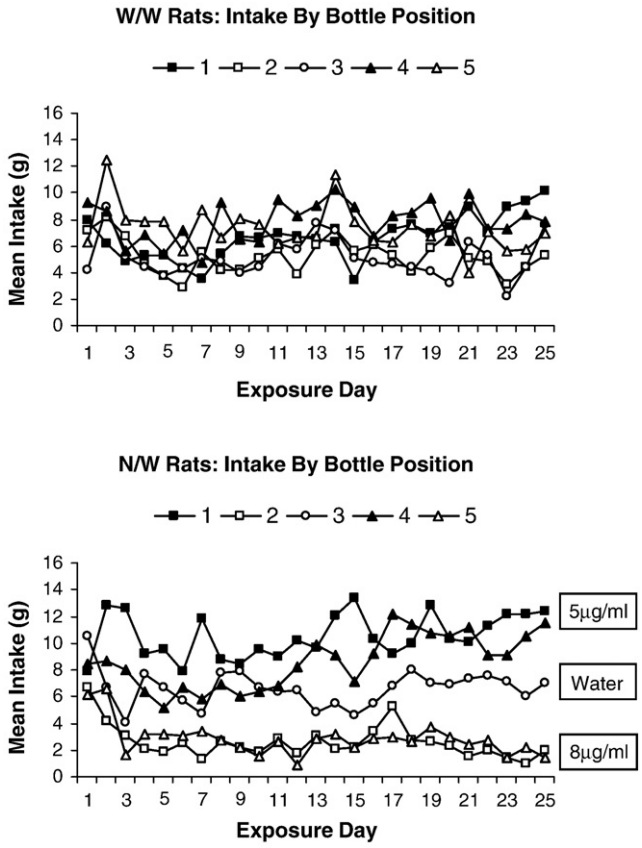

Fig. 1. Consumption by bottle position for rats having access to water only (W/W top panel) and rats having a choice between water and nicotine (N/W bottom panel). Data points represent mean daily intake scores (g) for 5 bottles available in home cages.

the previous 23 hour period. A cage of sham bottles matched to drinking condition N/W were filled and weighed using the same procedures to determine liquid loss due to evaporation and bottle handling. Bedding in all cages was checked thoroughly each day to determine incidence of bottle leakage. Evidence of bottle leakage resulted in no recorded intake scores for that subject that day and replacement of bottle and/or bottle cork. Leakage was easily detected upon daily inspection of bedding and occurred only once in this study.

2.3. Statistical analyses

Intake data were analyzed, using the software program SPSS, as a series of ANOVAs. The data were first analyzed, according to the study design as a 2 (drinking condition)×5 (bottle position)×25 (exposure day) mixed, multifactor design with the first two variables treated as between subjects independent variables and the fourth as a repeated measures factor. To address the possibility that bottle position would influence intake differently for rats in the two drinking conditions, as predicted, intake was analyzed for the two drinking groups in separate 5 (bottle position)×25 (exposure day) mixed factor ANOVAs. Intake for N/W rats was further analyzed to test for differences in consumption of the three solutions (water vs. 5 µg/ml vs. 8 µg/ml) by collapsing across bottles containing common solutions. A final analysis of intake by N/W rats was used to evaluate differences in the impact of bottle position during initial vs. terminal exposure days. We arbitrarily selected for the first and last 7 days of exposure for these analyses.

3. Results

Because bottles were placed in consistent positions for the duration of the study the amount of liquid (g) consumed from bottles in each position, for rats in each drinking condition, was analyzed to determine the influence of bottle position alone on intake. This analysis revealed no main effect of drinking condition, as rats in both exposure groups consumed, overall, comparable amounts of liquid. There were statistically significant main effects of bottle position $F(4, 56)=2.57$, $p<.05$ and day $F(24, 336)=3.24$, $p<.05$. Pair-wise comparisons revealed that overall, rats consumed more from bottles in positions 1 and 4 ($Ms=8.60$, 8.22 g respectively) than from bottles in position 2 ($M=3.92$); an effect primarily supported by intake patterns of rats in group N/W as will be presented. No other effects were statistically significant.

Despite no differences in overall consumption from individual bottles, there were clear differences in patterns of intake for rats with access to water only (W/W) vs. those with access to a water and nicotine solution choice (N/W). As shown in the top panel of Fig. 1, rats in condition W/W showed no clear pattern of discrimination between bottle positions. Mean intake scores from bottles 1–5 were comparable, $F(4, 28)=.813$, ns. However, as evident in the bottom panel of Fig. 1, rats in drinking condition N/W demonstrated a clear pattern of bottle discrimination, exhibiting relatively high intake from bottles in positions 1 and 4 ($Ms=10.54$ and 8.60) which contained the 5 µg/ml nicotine solution and relatively low intake from bottles in positions 2 and 5 ($Ms=2.57$ and 2.83) which contained the 8 µg/ml nicotine solution. The main effects of bottle position $F(4, 28)=2.71$, $p=.05$ and exposure day $F(24, 168)=2.60$, $p<.05$ were statistically significant but the interaction of bottle position×day was not. Follow up pair-wise comparisons confirmed that, overall, mean consumption from bottles 1 and 4 was significantly greater than consumption from bottles 2 and 5 ($p=.05$).

Closer examination of intake by N/W rats reveals that differences in intake from bottles in different positions did not occur immediately for these subjects. Rather, a clear pattern of discrimination between bottles containing the 5 µg/ml solution and those containing the 8 µg/ml solution developed with exposure. Only after day 11 does mean intake, from all bottles, show evidence of stability. To compare differences in bottle discrimination during initial and final exposure days, separate analyses of the first and last 7 exposure days were run. These analyses indicated no significant differences in intake by bottle position $F(4, 28)=2.32$, and no interaction between bottle position and day $F(24,168)=.87$ ns during the first 7 days of exposure. However, during the last 7 days of exposure there were significant differences in intake from different bottles $F(4, 28)=2.84$, $p<.05$ and a significant bottle position×day interaction $F(24, 168)=2.12$, $p<.05$. Again, rats consumed significantly more from bottles 1 and 4 than from bottles 2 and 5 ($p=.05$).

To formally test the hypothesis that rats in drinking condition N/W were discriminating bottle position based on content, the intake of each solution (5 µg/ml vs. 8 µg/ml vs. water) was compared across the 25 exposure days (Fig. 2). The analysis revealed significant main effects of solution $F(2, 14)=9.24$, $p<.05$ and day $F(24, 168)=2.567$, $p<.05$ and a

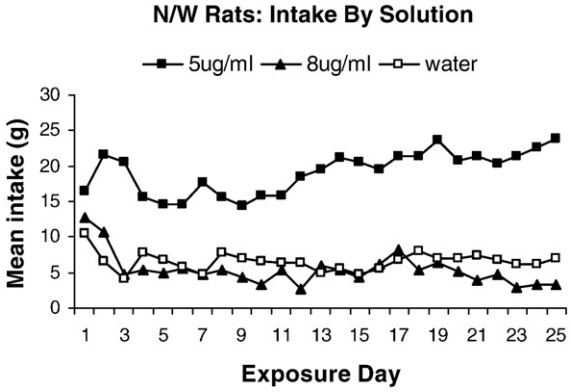

Fig. 2. Mean intake (g) of the three solutions available (water, 5 µg/ml, 8 µg/ml nicotine solutions) to rats in drinking condition N/W across the 25 days of exposure. The amount of the 5 µg/ml solution consumed was significantly greater than both water and the 8 µg/ml nicotine solution.

solution × day interaction $F(48, 336) = 1.441$, $p < .05$. As expected, rats drank more of the 5 μg/ml nicotine solution ($M = 19.14$ g) than the 8 μg/ml solution ($M = 5.40$ g) or water ($M = 6.64$). Pair-wise comparisons revealed intake of 5μg/ml was significantly greater than intake of 8μg/ml and water ($p < .05$).

4. Discussion

The goal of this study was to test the nicotine availability effect while providing rats with two concentrations of nicotine solution. It has already been established that rats, in general, do not demonstrate a preference for nicotine concentrations of 5 μg/ml and higher over water (Flynn et al., 1989). The resistance by rats to drink nicotine solutions is likely a key factor in the paucity of research using oral methods of nicotine self-administration with them. Earlier work in our laboratory revealed that female rats will drink significantly greater amounts of a 3 μg/ml nicotine solution with no manipulation other than increasing the availability of nicotine (Biondolillo and Pearce, 2007). The ability to augment voluntary nicotine consumption without resorting to deprivation seems a step in the direction of establishing oral methods as a means of investigating nicotine self-administration in rats.

The study reported here extends our earlier work by increasing solution concentration from 3 μg/ml to 5 μg/ml and adding a second, even more concentrated solution, as a choice. Rats clearly discriminated between the two nicotine solutions demonstrating that the influence of availability was tempered by factors associated with solution concentration. Rats developed a clear preference for the 5 μg/ml nicotine solution over water and the 8 μg/ml solution. It is important to note that both solutions were placed to the right and left of the water bottle, to discourage the formation of a left/right preference. This pattern of selective intake did not develop in control animals, drinking only water, suggesting that bottle contents were responsible for the effect. Thus, although the availability of nicotine presented in oral solutions contributes to voluntary consumption, factors associated with solution concentration are also determinants of intake.

Two primary features of nicotine solutions that would vary with concentration are taste features, as nicotine is thought to be bitter to rats (Smith and Roberts, 1995), and a complex of cues one could identify as post-ingestional responses to nicotine. These cues could range from feedback of digestive processes to potential changes in the central nervous system. Discrimination of solution concentration was not immediately evident in N/W rats; but, rather developed and stabilized with exposure. In fact, there were minimal differences in intake from bottles in different positions during the first 24 h of exposure for these rats. Assuming that oral cues associated with the solutions were evident immediately upon drinking this finding indicates that either the olfactory/gustatory features of the solutions were comparable or that none of the solutions were sufficiently bitter to promote avoidance. Early work on taste reactivity by rats to nicotine solutions suggests that initial taste reactions to nicotine concentrations of 1 μg/ml, 5 μg/ml 10 μg/ml and even 25 μg/ml were comparable to that of distilled water (Flynn et al., 1989). The data reported here are in line with this finding. Consistently higher levels of intake of the weaker nicotine solution became evident only with exposure; whereas consumption of water and the stronger nicotine solution remained comparable after the first day of exposure. This suggests that post-ingestional effects, produced by consumption of one or both solutions, were, in large part responsible for chronic intake patterns — an idea that has been around for some time (Davis and Levin, 1977; Flynn and Grill, 1988; Mook, 1963).

Studies wherein rats are given access to different concentrations of nicotine solution consecutively, indicate that rats will adjust solution consumption to maintain a relatively stable level of nicotine intake (Dadmarz and Vogel, 2003). Although we have no means of supporting that assumption directly, with these data it seems clear that some factor other than taste supported intake. That factor may be linked to the reinforced consumption of nicotine in the weaker solution or an avoidance of aversive consequences of drinking comparable levels of the stronger solution. One must also recognize that environmental availability exerted a probable influence on the consumption of both nicotine solutions as they were presented in two locations.

These results should be evaluated in light of weaknesses in the design and procedures used. An obvious limitation is evident in the fact that we used only female rats in this study. It has been demonstrated that sex contributes to reactivity or sensitivity to nicotine (Harrod et al., 2007; Park et al., 2007; Robinson et al., 2007). Although, we are confident that the data reported here stand alone and reflect an important relationship between environmental availability and voluntary consumption of oral nicotine, our goal is not necessarily to isolate the impact of oral nicotine on female rats. Rather, our use of females stems from practical and conceptual considerations stemming from earlier work with females, limitations of housing and manpower resources and current directions of the research program. One aim of the program is to use the voluntary methods replicated here to investigate the impact of maternal and early developmental nicotine exposure on offspring.

In conclusion, the data presented here, although preliminary, provide useful and important information and raise some interesting questions to researchers interested in the oral method of nicotine self-administration with the laboratory rat. First, the 2-bottle voluntary choice procedure is clearly not the best experimental arrangement if the goal is to increase the amount of nicotine rats will voluntarily consume. It remains to be determined if this effect is limited only by the number of bottles provided. Is it possible to augment nicotine intake even further by increasing number of available bottles containing nicotine? Second, the demonstration that adding a second concentration of nicotine solution (8 μg/ml) resulted in rats consuming higher levels of a concentration (5 μg/ml) that is known to support only relatively weak consumption raises more questions than answers. Could one support intake of any weaker nicotine solution, if given in contrast to a higher concentration solution? Are differential levels of intake of different nicotine solutions the result of simple approach/avoidance behaviors associated with specific differences in post-oral effects of the two solutions or is the contrast between effects of the two solutions influential? Finally, given recent evidence that adolescents express sensitivity to nicotine not seen in adults it would be interesting to compare the impact of the multiple bottle procedure on adolescent rats as compared to adults. One might anticipate an even greater effect of availability on the adolescent rat. These questions need to be further addressed in order to understand and differentiate the role availability, taste, and post-ingestional factors are playing in oral nicotine consumption. Luckily, the oral method lends itself readily to such questions.

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