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Taste and Nicotine as Determinants of Voluntary Tobacco Use by Hamsters[1]

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KSIR, C. *Taste and nicotine as determinants of voluntary tobacco use by hamsters.* PHARMACOL BIOCHEM BEHAV 19(4) 605–608, 1983.—Syrian hamsters consumed a commercial chewing tobacco in daily amounts equivalent to 2.6% of their body weights, even though food and water were always available. Daily intake increased gradually to this level over a period of 4 months. Commercial tobaccos contain a variety of flavoring agents, including sugars. Moistened, unflavored tobacco was consumed in much smaller amounts than the commercial tobacco. Addition of sucrose to the unflavored tobacco produced a concentration-dependent increase in daily consumption. Addition of nicotine to the drinking water did not affect daily fluid intake or food consumption, but produced a selective, dose-related decrease in consumption of the commercial tobacco. These results indicate interactive roles for taste and nicotine in controlling the daily, voluntary, high-level use of tobacco by hamsters.

Hamsters Tobacco Nicotine

ALTHOUGH per-capita use of tobacco for smoking has remained stable or shown a slight decline in the U.S. over the past 20 years, the use of "smokeless" tobacco has increased. In the decade from 1970 to 1980, U.S. sales of chewing tobacco increased from 1.06 to 1.38 pounds per adult male [7]. The use of these tobacco products is greater in some regions of the U.S. than in others, and in particular the "cowboy" traditions of the western and southern U.S. include the use of chewing tobacco. We recently conducted a survey among 314 undergraduate students at the University of Wyoming in which 27% of the males reported current use of smokeless tobacco, compared to 17.5% who currently smoked tobacco. Only 4.1% of the females reported current use of chewing tobacco. The only published data of which we are aware on tobacco chewing as a behavior was a 1981 report of smoking and chewing among 12–18 year olds in Nebraska, in which 7.1% of the males indicated current use of chewing tobacco [8].

We originally left some leaf-type chewing tobacco in a cage containing three female hamsters expecting that they might, in moving the tobacco, place it in their cheek pouches and perhaps absorb some nicotine. For about 30 minutes after the tobacco was placed in the cage the hamsters only sniffed at it when they passed it. The next day, the tobacco was gone from the cage. After several days it became clear that the hamsters were eating the tobacco. By this time, when fresh tobacco was introduced into the cage the animals would approach it, place it in their cheek pouches, carry it to a location away from the other hamsters, remove it from their pouches, and begin to eat it.

This phenomenon was of interest because we were unaware of any documented voluntary use of tobacco by nonhuman animals. There have been some anecdotal descriptions of the use of tobacco by captive nonhuman primates ([3], p. 423), but efforts to establish smoking behavior or nicotine self-injection in laboratory animals require elaborate instrumentation, prolonged training, and often require the use of some other reinforcing event when initiating tobacco or nicotine use [2, 5, 9].

EXPERIMENT 1

The first experiment was to examine whether every animal exposed to chewing tobacco would eat it, how much each animal would eat per day, and the effect of the tobacco on food and water intake and weight gain.

Animals

Twenty-four male golden Syrian hamsters weighing 70–90 g were placed in individual 29×19×13 cm polypropylene cages with wire tops. Purina lab chow was placed in a depression in the wire cage top, and water was freely available from a bottle placed on the cage top.

Method

The hamsters were randomly assigned to two groups of 12 each. After two days of adaptation to the cages, approximately 4 g of commercial leaf chewing tobacco (Beech-Nut) was placed in another depression atop the cages of half the animals. Each animal was removed from its cage at the same time each day, its cheek pouches were checked and anything in them removed with a blunt forceps, and the animal was weighed. The bedding was checked carefully for pieces of food or tobacco, and the bedding replaced. Water, food and tobacco were weighed and replenished. Each day a 4 g sam-

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ple of tobacco was left on a shelf so that loss of weight due to drying could be corrected for. These measures were collected daily for 10 days.

Results

During the first 10 days of daily measurments, the tobacco hamsters ate a mean of 1.1 g/day of tobacco, after correcting for evaporative loss. Every animal ate some of the tobacco every day, with individual 10-day means ranging from 0.6 to 2.0 g. There was no significant increase in tobacco consumption over that time period. Repeated-measures analyses of variance (ANOVAs) examined differences between the tobacco and no-tobacco groups for food intake, water intake, and body weight. Overall, the hamsters ate 7–8.5 g/day of lab chow, drank 12–14 ml/day of water, and gained a total of 13.9 g in body weight. Although there were no significant group differences for any of these measures, there was a slight tendency for the tobacco animals to eat less food and to gain more weight, probably reflecting the sugar content of the tobacco.

When the hamsters were exposed to tobacco for longer periods, the tobacco consumption increased. On days 28–38 the mean intake was 2.3 g/day, and there was a slow increase over that period. On days 128–139 the daily intake was relatively stable at a mean of 3.2 g/day (Fig. 1). Body weights at the end of the experiment averaged 125 g.

Discussion

This first experiment indicates that hamsters will eat chewing tobacco if it is made available, that they do so from the beginning in amounts over 1% of their body weight per day, and that over a four month period their intake increases to 2.6% of their body weight per day. Apparently all the animals eat tobacco, and it does not make them ill or interfere with their gaining weight. Although directly proportional body-weight comparisons with man should not be taken too seriously, it is striking to consider that a man weighing 70 kg would have to eat 1.8 kg of this tobacco each day to match the hamster's intake.

EXPERIMENT 2

In an effort to explain both the initial ready consumption of the chewing tobacco and the gradual increase in consumption over time, a working hypothesis was developed in which taste plays a role in the initial acceptance of the toabacco and the gradual increase over time is due to the development of a behavioral dependence on nicotine. An alternative explanation for the gradual increase is that nicotine absorption limits the amount of tobacco consumed right from the beginning, and a gradual tolerance develops to the aversive properties of nicotine. In either case, both taste and nicotine are assumed to be important factors controlling the amount of tobacco eaten by experienced hamsters.

The second experiment examined the influence of taste in controlling tobacco intake. The brand of tobacco used in the first experiment contains added sugars making up about 25% of the total weight of the product (approximately equivalent to 50 g sucrose for every 100 g of dry tobacco). Glycerin and water add moisture and account for most of the rest of the weight of the commercial product, with other flavorings (licorice, salt, and some that are not disclosed) contributing less than 5% of the total weight (personal communication).

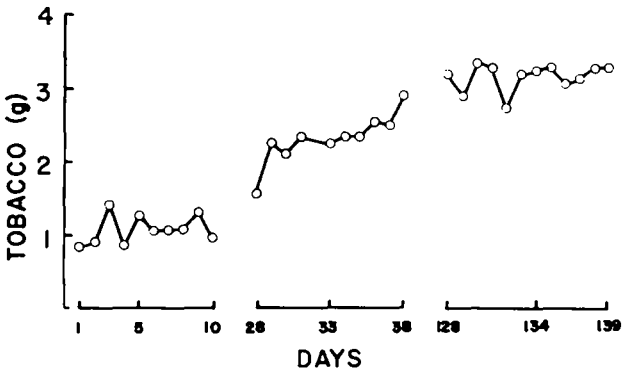

FIG. 1. Mean tobacco intake/day as a function of days of tobacco exposure. Each point represents a mean for 12 hamsters.

Animals

Twelve hamsters that had been eating the commercial tobacco for approximately three months were used in this experiment. They were housed, fed and watered as in Experiment 1.

Method

A supply of dry, unflavored tobacco was obtained from the manufacturer. This tobacco is the same blend as the commercial product, removed from the process prior to the application of the "casing" (liquid and flavorings). One preparation was made by adding 50 g sucrose, 60 g water, and 8 g glycerin per 100 g dry tobacco. Another preparation contained the same amounts of water and glycerin, but only 25 g sucrose. A third preparation contained the water and glycerin, but no sucrose. Four groups of three animals each were allowed to eat one of these three preparations or the commercial product for four days. Body weights, food, water and tobacco intake were measured daily as in Experiment 1.

Results

Since the different preparations contained different amounts of tobacco and water as proportions of their total weight, two corrections were necessary to make the intake values comparable. First, a sample of each preparation and of the commercial tobacco was left overnight on a shelf so that separate corrections for evaporation could be done for each type of tobacco. Second, the proportion of dry tobacco in each preparation was used to estimate the amount of Beech-Nut the animals would have eaten in consuming the equivalent amount of dry tobacco. These results are shown in Fig. 2. A mixed design analysis of variance (ANOVA) indicated that there were highly significant differences between the groups, $F(3,8) = 22.5$, $p < 0.001$. While the amount of intake was related to sugar content for the prepared tobaccos, the preparation with the highest sugar content, similar to the sugar content of the commercial tobacco, was not as well accepted as was the commercial product itself. There were no significant differences in food or water intake or body weight changes over the four day period.

Discussion

These results clearly indicate that the sweetness of the tobacco is an important determinant of the amount eaten. It

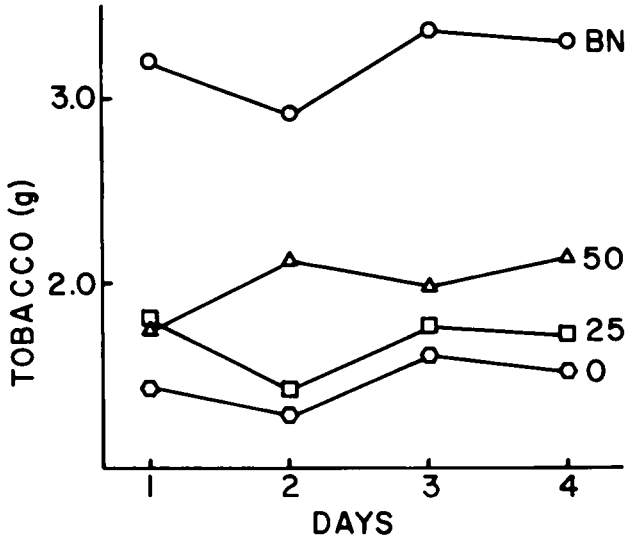

FIG. 2. Mean tobacco intake/day over four days of exposure to the commercial tobacco (BN), to an unflavored tobacco (0), or to unflavored tobacco with two levels of added sucrose (25,50). Each point represents a mean for 3 hamsters.

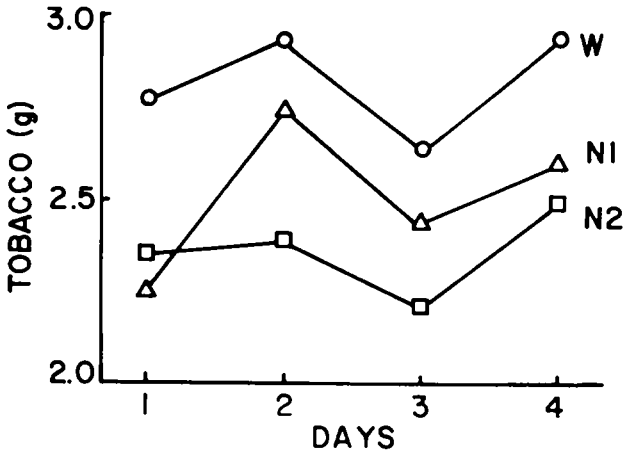

FIG. 3. Mean tobacco intake/day over four days of exposure to tap water (W) or one of two solutions of nicotine (N1, N2) in the drinking bottle. Each point represents a mean for 12 hamsters.

is perhaps fortunate that we initially chose to test a type of tobacco that contains so much added sugar and that we chose hamsters as subjects. Hamsters are apparently more sensitive to sweet tastes than are rats, for example, and in that respect more nearly resemble humans [1]. Although sweetness is important, the difference between the intakes of the sweetest tobacco preparation and the Beech-Nut indicates that the other flavorings contained in the commercial product, including salt, licorice, and proprietary ingredients, contribute significantly to the acceptance of Beech-Nut. Another important point is that animals in the 0 sugar group, which had been eating the commercial tobacco before this test, still consumed some tobacco even when it contained no added flavors at all.

EXPERIMENT 3

Two basic approaches have been used in studying the role of nicotine in cigarette smoking [6]. One approach is to vary the nicotine content of the tobacco, and another is to examine the influence of injected nicotine or nicotine chewing gum on amount smoked. Since the manufacturer of the chewing tobacco was unable to provide us with samples of tobacco varying in nicotine content, we used the indirect approach of adding nicotine to the hamsters' drinking water to determine if this would influence tobacco intake.

Animals

The same 12 hamsters that had been used in Experiment 2 were all allowed daily access to food, water, and the commercial tobacco for at least one week prior to the beginning of this experiment.

Method

The same commercial tobacco as used in the previous experiments was given daily to all the animals for 12 days, and measures of intake were the same as in Experiment 1. One group of four hamsters was given plain tap water in their drinking bottles. A second group of four was given a nicotine solution made by adding 1 ml of a 58% nicotine sulfate solution to 1 l. tap water. A third group was given a 2 ml/l solution of nicotine sulfate. These solutions are equivalent to 0.45 and 0.90 mg nicotine base per ml water. After four days, each group was switched to a different solution for four days, then switched again, so that at the end of 12 days each group had received each of the three solutions. The groups were exposed to the solutions in counterbalanced order.

Results

The data for all animals were combined for each solution conditon. Nicotine in the drinking water had no effect on fluid consumption, with the overall daily mean being 20.3 ml for water, 20.2 ml for the 0.45 mg/ml solution, and 19.2 for the 0.90 mg/ml solution, $F(2,22)=0.6$, n.s. Food intake was 6.4 g/day under the water condition, 6.0 g/day under the 0.45 mg/ml condition, and 5.9 g/day under the 0.90 mg/ml condition, also not a significant relationship, $F(2,22)=3.1$, n.s. The effect of nicotine on tobacco consumption is shown in Fig. 3. This decrease in tobacco consumption when nicotine was added to the drinking water was significant, $F(2,22)=8.0$, $p<0.005$.

Discussion

Adding nicotine to the water resulted in a decrease in tobacco intake, but not in fluid or food intake. The selectivity of the effect rules out the possibility that reduced tobacco intake is due to a general malaise or other nonspecific effect on consumption. This result implies that nicotine absorbed from the drinking water combines with nicotine absorbed from the eaten tobacco, and that the hamsters are regulating total nicotine intake within some upper bound. The tobacco used in these experiments contains about 0.5% nicotine by weight, so that a hamster eating 3 g/day would be taking in approximately 15 mg nicotine/day. The hamsters drinking 20 ml of 0.9 mg/ml nicotine solution consumed an average of 18 mg nicotine/day from the water, and reduced their tobacco intake by an average of 16%. The group drinking the weaker nicotine solution consumed an average of 9.1 mg nicotine/day from the water, and reduced their tobacco in-

take by 11%. Therefore, although the animals obtaining nicotine through the water did significantly reduce their tobacco intake, they still consumed more total nicotine than the animals drinking water. The estimated total nicotine intake was about 15 mg for the water group, about 24 mg for the weaker nicotine group, and about 30 mg for the stronger nicotine group.

GENERAL DISCUSSION

These experiments demonstrate that hamsters will consume large amounts of chewing tobacco, and that both taste and nicotine are important determinants of the amount of tobacco eaten. With regard to the idea that a nicotine dependence may develop in these animals, there are still some unanswered questions. The gradual increase in consumption over time may not be due to an increased dependence on nicotine but rather to an increasing tolerance to nicotine. Nicotine may influence consumption only by limiting the amount consumed, and the hamsters may be eating the tobacco only because of its flavor. We have received a sample of denicotinized chewing tobacco with added flavorings similar to the commercial tobacco. Preliminary indications are that hamsters that have been eating the commercial tobacco eat much less of this denicotinized tobacco when it is substituted. While the denicotinized tobacco seems to have a similar flavor to humans, it cannot be ruled out that its flavor is sufficiently different from the commercial tobacco for the taste change to account for the decreased consumption seen in hamsters switched from the commercial tobacco to the denicotinized. Our finding in Experiment 2 that hamsters switched from commercial tobacco to an unflavored tobacco will still consume a small amount of the tobacco is a further indication that taste alone may not be maintaining this tobacco intake. Further evidence on these questions will come from long-term intake studies with tobacco-naive animals started on unflavored or on denicotinized tobacco.

Gastrointestinal absorption of a drug is followed by passage through the liver before entering the general circulation. Nicotine is subject to rapid liver metabolism, and this has led to the statement that "because of first-pass metabolism in the liver, nicotine absorbed through the gut after ingestion has little pharmacological effect compared with nicotine absorbed by routes such as the skin, nasal and buccal mucosae, lungs, and even the rectum, all of which allow the nicotine to be distributed in the general circulation before passage through the liver" [10]. It is therefore appropriate to ask whether meaningful blood levels of nicotine are produced in these hamsters after ingestion. One hamster that had been eating tobacco for several weeks was given a 2-g sample of tobacco for 30 minutes, during which time 0.37 g were consumed. The animal was then sacrificed by decapitation so that a large enough blood sample could be obtained for assay. The blood sample, along with a coded control sample taken from another hamster not exposed to tobacco, were frozen and shipped for assay. The assay found no nicotine in the control sample, and 43.9 ng nicotine/ml plasma in the sample from the hamster that had eaten tobacco. This value is just above the mean blood levels reported for human oral smokeless tobacco users by Gritz *et al.* [4], is above the levels reported for cigar smokers and about the same as the peak levels reported for nasal snuff users [11].

It appears that the hamster may provide a useful model for studying the acquisition of tobacco use, factors influencing tobacco use, and some of the physiological effects of tobacco use. Since significant blood levels of nicotine may be produced using this model, the effects of nicotine on cardiovascular function, development, and reproduction may be studied without elaborate smoking machines and without the need to repeatedly inject nicotine.

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