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Microinjections of Dopaminergic Agents in the Nucleus Accumbens Affect Ethanol Consumption But Not Palatability

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KACZMAREK, H. J. AND S. W. KIEFER. *Microinjections of dopaminergic agents in the nucleus accumbens affect ethanol consumption but not palatability.* PHARMACOL BIOCHEM BEHAV **66**(2) 307–312, 2000.—It was determined whether ethanol palatability in rats could be changed by manipulating the reinforcement experienced during limited access consumption. During the first 3 days of the experiment, initial taste reactivity (TR) testing to distilled water (1 day) and 10% alcohol (2 days) was performed. Following the establishment of baseline TR, separate groups of animals received bilateral microinjections (0.5 μl/side) into the nucleus accumbens of either the nonspecific dopamine agonist *d*-amphetamine sulfate (20 μg, $n = 10$), the D_2 antagonist raclopride (1.0 μg, $n = 8$), or physiological saline ($n = 5$). The injections occurred at the same time each day for 5 consecutive days. Five minutes after the microinjection, the fluid-deprived rats were given 30-min access to 10% ethanol. Over the 3 days following drug administration, TR to distilled water and 10% alcohol was repeated. After this, the rats were once again given 30 min of access to 10% ethanol for 5 consecutive days, but without drug microinjection prior to alcohol access. A final TR exposure (the same as the others) was performed over the final 3 days of the study. Both raclopride and *d*-amphetamine administration produced reductions in ethanol consumption (in comparison to saline treatment). However, treatment with *d*-amphetamine and raclopride during ethanol consumption did not cause significant, conditioned changes in palatability as measured by the taste reactivity procedure. These results suggest that dopamine plays a role in the motivation to consume ethanol but this neurotransmitter is not involved in evaluating its incentive value. © 2000 Elsevier Science Inc.

Dopamine Nucleus accumbens *d*-Amphetamine Raclopride Taste reactivity Ethanol consumption Rats

THE role of the mesoaccumbens dopamine (DA) pathway in the reinforcing properties of ethanol (EtOH) has generated considerable interest. Brain dialysis studies have determined that systemic injections of EtOH increase the amount of DA and its metabolites in the nucleus accumbens (NAC) of rats (6,8,25). Due to the fact that EtOH causes an increase in DA release and metabolism in the NAC, some investigators have suggested that local DA activity may play an important role in EtOH reinforcement (16,19,20). Further evidence in support of this proposition has been found by way of dialysis research in which the perfusion medium included EtOH. Extracellular concentrations of DA in the NAC increased significantly over baseline values when doses as low as 0.1% EtOH (v/v) (24) and 50 mM EtOH (25) were included in the perfusate. Furthermore, dihydroxyphenylacetic acid levels were increased after perfusion with 100 mM EtOH (25).

Direct systemic injections of dopamine agonists and antagonists including the nonselective receptor agonist apomorphine (15), the reuptake blocker bupropion (22), the D_1/D_2 receptor agonist SDZ-205, 152 (17), the nonspecific agonist amphetamine (22), the D_2 antagonist haloperidol (15,22), the D_1/D_2 antagonist fluphenazine (16), and the D_2 antagonist pimozide (22) have reduced self-administration of EtOH. Limited access consumption of EtOH was not affected by systemic ad-

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ministration of amphetamine, the D_2/D_3 receptor agonist quinpirole, the D_1 receptor blocker SCH 23390, or the D_2 receptor blocker spiperone (11). The D_2 antagonist pimozide had no effect on free-choice consumption of EtOH (5). Overall, dopaminergic agonists and antagonists, when administered systemically, have been shown to cause a decrease in self-administration, but have no effect on free-choice or limited access consumption.

Although systemic administration of DA agonists and antagonists have both resulted in decreases in self-administration of EtOH, microinjection of these substances directly into the NAC has led to relatively consistent and characteristic patterns of responding for the different treatments. Specifically, intra-accumbens injection of the DA agonist *d*-amphetamine (7,20) or quinpirole (7) resulted in a constant, steady self-administration response rate throughout the session leading to an increase in total session responding but an overall decrease in the rate of responding.

The pattern of responding changed quite dramatically when the D_2 DA antagonist raclopride was microinfused into the accumbens. With raclopride, an overall decrease in total session responding for EtOH occurred in a dose-dependent manner (19). Low dose microinjections of raclopride did not disrupt the early high rate of responding characteristic of EtOH self-administration, but at higher doses, the early fast-paced responding was somewhat delayed. Whether high rate responding began immediately at the start of the session or was delayed, it terminated soon after it began, suggesting the decrease in overall responding and response rate was due to a blockade of EtOH's reinforcing effects.

In addition to reinforcing properties, the decision to drink EtOH is based on a number of different factors. Particularly, the taste of EtOH plays a pivotal role in whether a particular solution is consumed (9). After a period of EtOH access, rats show an increase in the palatability of EtOH as determined by the taste reactivity test (10), suggesting that prior EtOH experience is an important factor in determining its palatability. Other researchers have discussed the possibility that the environmental cues (such as taste and smell) of EtOH paired with the reinforcing effects of DA release that occur during early EtOH consumption could eventually lead to a conditioned DA release brought on by the taste and smell factors of the EtOH alone (21). In other words, the continual pairing of the taste of EtOH with the DA release that occurs postingestion could eventually result in a conditioned release of DA occurring as soon as the EtOH is tasted by the animal. This conditioned DA release could potentially explain the decrease in aversive reactivity responses that rats exhibit after a period of access to EtOH (10).

Rats have been trained to prefer the bitter taste of a sucrose octaacetate (SOA) solution as a result of administration of an intragastic loading of a nutritive polycose as the animal voluntarily drank the SOA solution (12). During training, each rat also received an intragastric loading of water while voluntarily drinking a sour-tasting citric acid solution. Once training was completed, microdialysis samples were collected from the NAC prior to, during, and after presentation of each taste solution. Presentation of the sucrose octaacetate solution significantly increased extracellular DA in the animals during the 30 min following its presentation. Dopamine levels were not altered after presentation of the citric acid solution or in animals that did not receive conditioning. These results suggest that a conditioned DA release may occur to the taste of a solution alone as a result of prior conditioning between the taste and postingestional effects.

The purpose of the present study was to determine if the palatability of EtOH would be influenced by the presumed reinforcement experienced during EtOH consumption. Although free access is often argued to be a better indicator of alcoholism, the animals tested in the present study were given restricted access to EtOH so as to have control over when reinforcement was allowed to be experienced. Because DA release is argued to be an important aspect in the reinforcing properties of EtOH consumption, the present study attempted to manipulate the amount of reinforcement experienced by presenting the DA agonist, *d*-amphetatmine, to facilitate reinforcement and presenting the DA antagonist, raclopride, to block reinforcement. Due to the fact that self-administration is argued to be another good indicator of reinforcement, the dosages of *d*-amphetamine and raclopride selected to induce such manipulations were chosen based on their ability to increase and decrease self-administration for EtOH, respectively (19). Likewise, it was predicted that the doses of *d*-amphetamine and raclopride used in the present study would increase and decrease alcohol consumption, respectively, in comparison to saline animals.

The taste reactivity procedure was used to determine if the palatability of EtOH changed as a result of conditioning between the taste of EtOH and its reinforcing effects (DA release) experienced during consumption. If the taste of EtOH was associated with the reinforcing effects of its consumption, those animals that received *d*-amphetamine would increase ingestive responding and decrease aversive responding in the taste reactivity test. The animals that received raclopride would experience less reinforcement associated with consumption, and would, therefore, show less ingestive responding and more aversive responding during taste reactivity testing than the *d*-amphetamine-treated animals.

METHOD

Subjects

The subjects were 36 male Long–Evans rats (Harlan, Indianapolis, IN). The animals were approximately 250–300 g upon arrival, and were individually housed in a room with a normal 12-h light/dark cycle (lights on 0700–1900 h). Food and water were continuously available except when the animals were on a restricted fluid access schedule.

Surgery

Rats were anesthetized with sodium pentobarbital (Nembutal, 50 mg/kg IP) and mounted in a stereotaxic headholder (Kopf) to immobilize the head for cannula implantation. Two 22-gauge stainless steel guide cannula (Plastics One, Roanoke, VA), 6 mm in length, were implanted, aimed 1.0 mm above the NAC injection site (one within each hemisphere). The stereotaxic coordinates for the guides were: anterior +1.7 mm, lateral ±1.2 mm to bregma, and ventral −5.5 mm from the skull surface (13). The cannula were secured on the skull with mounting screws and dental cement; wire stylets were inserted to prevent blockage. Following implantation of the cannula, the rat was removed from the stereotaxic headholder and implanted with an intraoral fistula made of 100-gauge polyethylene (PE) tubing. The nonflared end of the tubing was placed on a needle, inserted into the animal's mouth lateral to the first maxillary molar, and then threaded subcutaneously along the rat's cheek to exit at the top of the scalp posterior and lateral to one of the cannula. The tubing was pulled taut until the flared end of the fistula (inside the animal's mouth) fit into place.

This position was maintained by tightening a teflon washer placed over the nonflared end of the fistula on top of the animal's head. The nonflared end was then trimmed and a metal tip attached to it. All rats received 0.15 cc of bicillin (IM) to prevent infection, and were given a minimum of 5 days for recovery.

Drugs and Microinjection

To acclimate the rats to the injection procedure, each rat received an initial microinjection of physiological saline. While the unanesthetized animal was gently restrained, stylets were removed and the 28-gauge bilateral injectors were lowed through the guide cannula to terminate at the injection site 1.0 mm below the end of the guides. The pump was equipped with two syringes (one syringe per cannula) and was driven at a rate of 0.5 μl/min to deliver a total volume of 1.0 μl/brain (0.5 μl/side). After an additional min of diffusion time had elapsed, the injectors were removed, and the stylets were reinserted.

Separate groups of animals received either the nonspecific DA agonist *d*-amphetamine sulfate (20 μg/brain) (Sigma, St. Louis, MO), the D_2 antagonist raclopride (1.0 μg/brain) (RBI; Natick, MA), or physiological saline at the same time each day for 5 consecutive days using the same procedure described above. All drugs were dissolved in physiological saline.

Taste Reactivity Apparatus

The rats' responses to distilled water and 10% ethanol (v/v) were measured several times during the experiment using the taste reactivity procedure. The taste reactivity chamber was a Plexiglas cylinder that rested on a glass base placed above a mirror such that the animal's ventral side could be recorded by a videocamera focused on the mirror. One end of 100-gauge PE tubing was connected to a 10-cc glass barrel syringe mounted on an infusion pump. The tubing was filled with the appropriate solution to eliminate dead space, and the other end was attached to the metal tip of the animal's fistula, thus allowing fluid to be delivered directly into the animal's mouth (rate = 0.84 ml/min). The infusion pump and an electronic timer were initiated simultaneously so that the start of infusion marked the start of each trial. The animal's taste reactivity responses to a 1 min infusion of solution were recorded. Specifically, orofacial responses and body movements were videotaped using a D5000 Panasonic camera equipped with an 8:1 autofocus zoom lens connected to a BR-7700U JVC video cassette recorder with the time code generator.

Procedure

Habituation. Following postoperative recovery, rats were habituated to the taste reactivity testing chamber. Each rat was removed from its home cage and placed in the testing apparatus for 3 min on 3 consecutive days. On the last day of habituation, each rat received a 1-min infusion of tap water at the end of the period to acclimate it to the infusion procedure. Immediately after the last habituation period, the rats were returned to the colony room where each rat received a microinjection of saline into the NAC.

Taste reactivity testing. On the first day following habituation, each animal was tested for taste reactivity to distilled water. Taste reactivity testing to distilled water also occurred on experimental days 9 and 17. On the 2 days following taste reactivity testing to distilled water (experimental days 2, 3, 10, 11, 18, and 19), all animals were tested for taste reactivity to 10% ethanol, one trial per day.

Restricted access. Starting at habituation, the rats were placed on a restricted access drinking schedule, which remained in effect throughout the remainder of the experiment. Every day the animals received two periods of access to fluid. The first access period was at 0945 h, and was 30 min in length. This access period consisted of distilled water except on experimental days 4–8 and 12–16, during which 10% ethanol was presented. On experimental days 4–8, each rat received its assigned microinjection 5 min prior to ethanol access. Once presented with the ethanol solution, the amount of ethanol consumed at the end of the 30-min period was recorded to the nearest 0.5 ml. The protocol during days 12–16 was identical to that occurring during days 4–8, with the exception that the animals did not receive any drug microinjection prior to ethanol access. The second access period occurred at 1200 h, was 60 min in length, and always consisted of distilled water. On days in which the animals were tested for taste reactivity, they received distilled water during both access periods. Taste reactivity testing occurred immediately after the first access period at approximately 1030 h.

Histology

When all testing was completed, animals were given an overdose of Sleep Away and transcardially perfused first with 0.9% saline followed by 10.0% formalin. The brains were then removed, sliced, and stained with cresyl violet to verify injector cannula placements.

Videotape Analysis

Following taste reactivity data collection, the videotaped trials were analyzed frame by frame to classify and record the responses made by each subject. Every trial was scored with the experimenter blind to the animal's treatment condition. Responses recorded as ingestive included tongue protrusion (midline extension of tongue), lateral tongue protrusion (unilateral extension of tongue), and mouth movement (rhythmic, low-amplitude openings of the mandible). Aversive responses included gape (retraction of the corners of the mouth resulting in wide opening of the mouth), forelimb flail (rapid movement of forelimb from side to side), head shake (rapid movement of the head from side to side), paw pushing (alternating movements of front paws on the glass floor), drip (loss of fluid from animal's mouth to the floor), chin rub (contact between chin and chamber floor as animal propelled forward), and fluid expulsion (active rejection of fluid often associated with forelimb flails and head shakes). Bouts of paw licking, a neutral response, were also recorded.

Statistical Analysis

The 30-min ethanol and 60-min water consumption data were analyzed using separate $3 \times 2 \times 5$ (group × condition × day) mixed ANOVAs with the variables condition and day serving as the repeated-measures factors. The variable group referred to the three treatment groups included in the experiment: *d*-amphetamine, raclopride, and saline. The variable condition referred to whether the animals were or were not receiving microinjection prior to the 30-min access period to ethanol. The variable day referred to the 5 days contained within each condition.

The total ingestive and total aversive taste reactivity responses to distilled water were analyzed separately using 3×2 (group × exposure) mixed ANCOVAs. The data collected during baseline TR served as the covariate, while the data from

the first and second exposures were the repeated measures. The total ingestive and total aversive taste reactivity responses to ethanol were also analyzed separately using 3 × 2 (group × exposure) mixed ANCOVAs. The reactivity data collected over the 2 days of ethanol within the baseline TR and each of the later TR exposures were averaged separately to yield one data value per animal for the baseline TR and for each of the two TR exposures. The assumption of homogeneity of the within-class regression coefficients that underlies ANCOVA was tested by calculating the exposure by covariate interaction. When the interaction was not significant, its respective sum of squares and degree of freedom were pooled with the within-subjects error term. If the interaction was significant, the sum of squares and degree of freedom were left partitioned out of the within-subjects error term to retain power.

When significant effects were found, post hoc tests were performed using the Dunnett procedure (23) to determine if the treatment groups differed significantly from the saline animals. A level of significance equal to 0.05 was used for the post hoc tests.

RESULTS

Of the 36 animals that began the experiment, the data from 13 animals were excluded due to loss of fistula viability and subject attrition. The data from one additional animal was excluded due to bad cannula placement. The final number of subjects within each group was as follows: *d*-amphetamine ($n = 10$), raclopride ($n = 7$), and saline ($n = 5$). Injection locations tended to cluster just inside the dorsal edge of the NAC for all experimental groups.

Ethanol

Statistical analysis of the ethanol consumption data revealed a significant main effect of group, $F(2, 19) = 3.43$, $p = 0.053$, a significant main effect of condition, $F(1, 19) = 15.46$, $p < 0.01$, and a borderline significant interaction between group and condition, $F(2, 19) = 3.33$, $p = 0.058$. As can be seen in Fig. 1, consumption by the *d*-amphetamine- and raclopride-treated animals was reduced in relation to that of the saline animals. Post hoc Dunnett tests indicated that both the *d*-amphetamine- and raclopride-treated animals were significantly different from the saline-treated animals during drug treatment ($p < 0.01$). Despite the opposite effects on dopaminergic receptors, both drugs decreased ethanol consumption. When administration of the drugs was discontinued, consumption levels of the previously drug treated animals immediately returned to the level of the saline group.

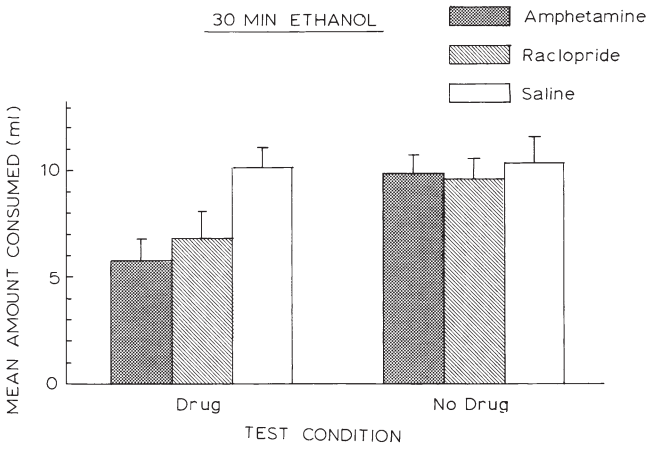

FIG. 1. Mean amount of 10% ethanol consumed during 30-min restricted access collapsed across 5 days of drug treatment and 5 days of no drug treatment.

Statistical analysis of the ingestive taste reactivity responses to alcohol (see Fig. 2 top) revealed a significant main effect of group, $F(2, 18) = 3.66$, $p < 0.05$. This effect was driven primarily by the saline group that made the most ingestive responses. Post hoc Dunnett tests revealed that the saline animals made significantly more ingestive responses than both the *d*-amphetamine and raclopride groups ($p < 0.01$). Figure 2 (bottom) also shows the aversive taste reactivity responses made to ethanol. The exposure by covariate interaction was significant, $F(1, 18) = 9.47$, $p < 0.01$; therefore, the sum of squares and degree of freedom were left out of the within-subjects error term. Despite the apparent decrease in aversive responding by all three groups from exposure 1 to exposure 2, the statistical analysis revealed no significant effect of exposure. Similarly, the group and group by exposure factors were statistically nonsignificant.

Distilled Water

Consumption data for the 60-min water access are presented in Fig. 3. Statistical analysis revealed a significant main

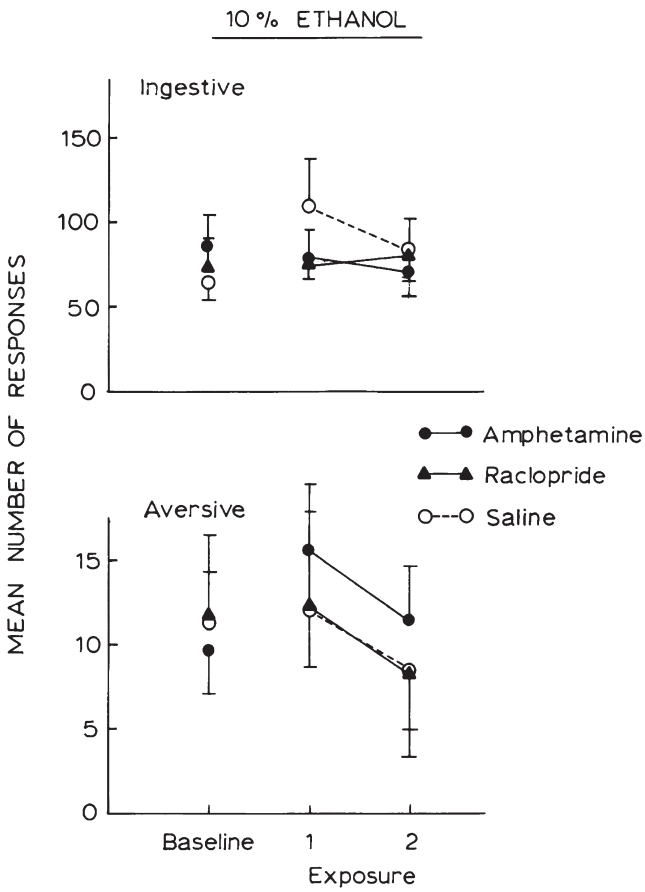

FIG. 2. Mean number of ingestive (top) and aversive (bottom) responses to 10% ethanol. The single points indicate baseline levels of responding for each group. Exposure 1 refers to testing that occurred following the 5 days of drug treatment. Exposure 2 refers to testing that occurred following the 5 days of no drug treatment.

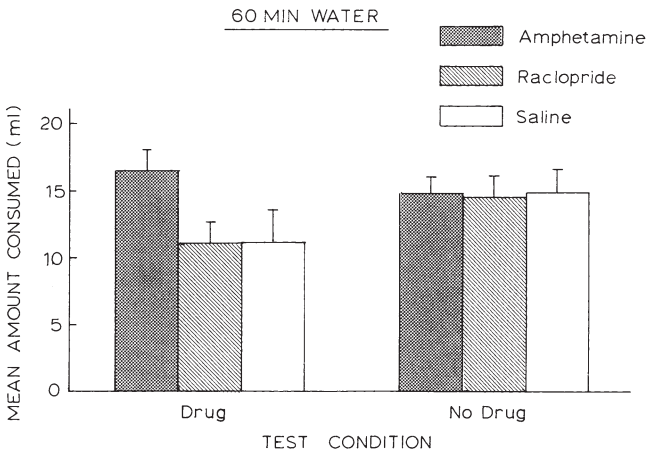

FIG. 3. Mean amount of distilled water consumed during 60-min restricted access collapsed across 5 days of drug treatment and 5 days of no drug treatment.

effect of condition, $F(1, 19) = 6.71$, $p < 0.05$, and a significant interaction between group and condition, $F(2, 19) = 7.24$, $p < 0.01$. The mean amount of water consumed (±SEM) during the 2 days prior to drug treatment was approximately the same for all three groups: 9.80 ± 0.99 for *d*-amphetamine, 9.39 ± 1.03 for raclopride, and 9.40 ± 1.51 for saline. However, once drug treatment was administered, the *d*-amphetamine animals showed an increased level of water consumption while the raclopride and saline animals drank amounts similar to what they consumed prior to drug treatment. Post hoc Dunnett tests revealed the increase in water consumption by the *d*-amphetamine animals to be statistically significant ($p < 0.01$). The total amount of fluid consumed across groups was higher overall during the 5 days when no drug treatment was given.

Lastly, analysis of the total ingestive responses to distilled water yielded no significant effect of group, exposure, or interaction of group by exposure. Analysis of the aversive responses determined the interaction of exposure by covariate to be significant, $F(1, 18) = 19.27$, $p < 0.01$. The effect of exposure approached significance, $F(1, 18) = 4.27$, $p = 0.053$, using the nonpooled within-subjects error term. Subjects made fewer aversive responses overall during the second exposure. The main effect of group and the interaction of group by exposure were not statistically significant.

DISCUSSION

The doses of *d*-amphetamine and raclopride tested in the present study had a clear effect on ethanol consumption but did not appear to have an effect on ethanol palatability. Although it was expected that the nonspecific DA agonist *d*-amphetamine would increase consumption and the D_2 antagonist raclopride would decrease consumption, the present study found that microinjection of either substance into the NAC resulted in a decrease in ethanol intake compared to saline-treated animals. This evidence suggests that DA plays a complex role in the reinforcing properties of alcohol, because manipulation of DA levels within the NAC influenced how much alcohol was willingly consumed.

It was somewhat surprising that both the agonist and antagonist, which were expected to have opposite effects when microinjected, had similar effects on alcohol consumption (see Fig. 1). When presented systemically, both DA agonists (15,17,22) and antagonists (15,16,22) have been shown to decrease self-administration. These results would seem to support the findings of the present study. However, self-administration studies involving microinjections of the same drug dosages as the current study directly into the NAC have found increased responding due to *d*-amphetamine administration and decreased responding due to raclopride administration (19). It should be pointed out that while these studies measured self-administration, the present study measured consumption so the difference in results may be due to differences in procedure (i.e., systemic vs. microinjection, self-administration vs. consumption testing). Future research is planned to test this hypothesis.

One possibility is that the dose of *d*-amphetamine tested was strong enough to raise DA levels so high that the reinforcement experienced was maximal and could not be advanced by further alcohol consumption. Namely, administration of *d*-amphetamine resulted in a "ceiling effect" such that animals failed to drink increased amounts of alcohol, because doing so did not advance their reinforcement experience. On a related note, even if the *d*-amphetamine did not push DA levels to the "ceiling," the agonistic properties of the drug may have caused a substantial enough amount of DA to be released from the presynaptic terminal such that any additional increases in DA-mediated reinforcement at the postsynaptic receptors due to EtOH consumption were concealed. This "masking" effect has been proposed in previous research where the direct DA D_1 agonist SKF81297 has been shown to increase brain stimulation reward thresholds (1). The authors argued that administration of the D1 agonist binds to postsynaptic receptors and acts as a type of "noise" that makes the DA signal resulting from self-stimulation more difficult to detect.

It is also possible that the *d*-amphetamine animals decreased their consumption because presentation of the drug created a state of negative hedonia in these animals. Previous research has determined that increases in dopamine levels within the NAC have occurred in response to aversive stimuli (18). In other words, the *d*-amphetamine may have successfully increased dopamine levels within the NAC, but this did not necessarily enhance their EtOH reinforcement. This conclusion is somewhat suspect, considering that the exact dose of *d*-amphetamine used in the current study produced increases in self-administration for EtOH in past research (19).

The differences seen in the water consumption data suggest that although *d*-amphetamine and raclopride had similar effects on ethanol consumption, they did produce differential effects on water intake (see Fig. 3). Specifically, while the animals were receiving drug injections, both groups decreased their alcohol consumption. However, the *d*-amphetamine group compensated for the decrease by increasing the amount of water they drank during the 60-min access period. The raclopride group did not show this compensation in water intake during drug administration, and instead, remained at a level similar to that of saline animals.

Although differences in ethanol consumption were clear, differences in the taste reactivity data for ethanol were not as apparent. Although the ingestive taste reactivity data did show a main effect of group, this effect was due primarily to the large number of ingestive responses made by the saline treated animals (see Fig. 2). Of particular interest is the fact that the number of ingestive responses made by both the *d*-amphetamine and raclopride groups remained stable over both exposures. Even though the treatment groups drank less

ethanol during consumption, manipulation of the reinforcement experienced during consumption did not appear to have any conditioned effects on palatability.

Although the present study was done to investigate if manipulation of DA levels had conditioned effects on palatability, other studies have administered dopaminergic agents on the same day prior to taste reactivity testing. Research has investigated whether the D_2 receptor blocker pimozide would change the palatability of a sucrose or quinine solution (14). Results indicated that pimozide administered intraperitoneally did not cause a change in palatability because overall taste reactivity responding was not changed. Similar results have been found in a lesion study where injections of 6-OHDA were administered into the ascending dopaminergic bundle (4). Dopamine depletion in the NAC and neostriatum was found to be greater than 99% in all rats tested. Although the rats with lesions were aphagic, their taste reactivity responses to sucrose and quinine were the same as the control animals. This finding provides further evidence that DA does not play a role in determining palatability. Hence, the fact that DA manipulation failed to have any conditioned effects on palatability in the current study appears to be consistent with prior work.

A reward system composed of two separate components has been proposed to address the disparity that is often present between palatability and consummatory data (2). According to the hypothesis, there is an affectual component that is a measure of palatability, as well as a motivational component that is more indicative of appetite. It has been argued that instrumental measures, such as self-administration and voluntary consumption, are more indicative of the motivational component, although not necessarily independent of palatability (3). For this reason, such measures should not be used to measure hedonic properties of a stimulus because they do not solely indicate palatability. The responses elicited by the taste reactivity procedure are a good indication of the affectual qualities of a substance because these responses are not instrumental. Using this information, the incompatibility between the ethanol consumption and taste reactivity data of the current study seems to make sense. Dopaminergic manipulation can change the instrumental component of ethanol as seen by decreased consumption in the current study and changes in self-administration (15–17,19,22). However, changes in DA levels do not seem to have an effect on the palatability of ethanol, as shown by the results of the current study and results of other studies measuring taste reactivity (4,14).

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