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Effects of Intraaccumbens Injections of Dopamine Agonists and Antagonists on Sucrose and Sucrose-Ethanol Reinforced Responding

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HODGE, C. W., H. H. SAMSON, G. A. TOLLIVER AND M. HARAGUCHI. *Effects of intraaccumbens injections of dopamine agonists and antagonists on sucrose and sucrose-ethanol reinforced responding.* PHARMACOL BIOCHEM BEHAV **48**(1) 141-150, 1994.—The present experiment tested the effects of intraaccumbens injections of dopamine (DA) agonists and antagonists on operant responding reinforced by sucrose and sucrose/ethanol solutions. The mixed DA agonist *d*-amphetamine (20.0 μg/μl) significantly reduced responding reinforced by a low concentration sucrose solution (2% w/v) by 48% and 38% compared to no injection and sham control values, respectively. The addition of ethanol (10%) to a low concentration sucrose solution (3%) presented as the reinforcer changed the response pattern from a continuous moderate response rate, over a 30 min session, to an initial high response rate that terminated after approximately 10 min. With sucrose/ethanol reinforcement, *d*-amphetamine slowed the initial high response rate but extended responding throughout the 30 min sessions. However, no significant changes were observed in number of responses per session. When 75% sucrose (w/v) was presented as the reinforcer, *d*-amphetamine did not change the total number of responses/session, but response patterns were again altered from high initial rates with early offset to slow steady rates that continued for the duration of sessions. The D_2 DA antagonist raclopride (0.1-5.0 μg/μl) resulted in a dose-dependent decrease in responding reinforced by 75% sucrose. The baseline patterns, response totals, and effects of the DA antagonists resemble our previously reported findings with 10% ethanol (v/v) reinforcement. These data support the conclusion that mesolimbic DA activity may be a common mechanism in ethanol reinforced behavior and behavior reinforced by other substances, but suggest that the nature of behavioral change may depend upon the reinforcer.

Ethanol Ethanol reinforced behavior Sucrose Nucleus accumbens Microinjection Dopamine Rats

THE mesolimbic-mesocortical DA systems has been hypothesized to serve a general role in reinforcement by all drugs (5,37) as well as integrating various types of motivated behavior (16). Clearly, the mesolimbic-mesocortical dopamine (DA) systems have been shown to play a prominent role in the maintenance of behavior reinforced by stimulant drugs (14,15, 36,38). Microinjection of DA antagonists directly into n. accumbens alters IV self-administration of both amphetamine and cocaine, supporting the hypothesis that DA activity in this system is important for the maintenance of stimulant drug self-administration behavior (14). Similarly, DA agonists microinjected into the n. accumbens have been shown to function as reinforcers, suggesting that activation of the DA system is potentially part of the mechanism maintaining drug self-administration behavior (10).

The specific role of this system in the reinforcing properties of other drugs remains unclear (7,14,16). For example, 6-OHDA lesions affect stimulant self-administration but do not alter opiate or alcohol self-administration (18,22,28,29,30). However, reducing DA transmission in this pathway through

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direct injections of the DA antagonists raclopride (33,34) and fluphenazine (27) in n. accumbens, and the D_2 agonist quinpirole in the ventral tegmental area (11), decrease ethanol reinforced responding.

Another line of evidence implicating the mesolimbic DA system in the regulation of self-administration behavior comes from findings of increased extracellular DA levels following the administration of many abused drugs (6,13). However, the role this activity might play in regulating ethanol self-administration behavior is unclear. Systemic administration of *d*-amphetamine and apomorphine decreased ethanol reinforced responding as a result of a major slowing and disruption of the normal response pattern (23,24). However, increasing extracellular DA by direct injection of *d*-amphetamine in n. accumbens increased ethanol reinforced responding by slowing response rates but extending the duration of responding for periods of up to 1 h (12,32-34). The extent to which these effects specifically involve the n. accumbens and whether they are exclusively involved in the regulation of ethanol reinforced behavior, however, remains to be elucidated.

A variety of evidence suggests that behavior controlled by other reinforcers, such as sucrose or food, may be regulated by the mesolimbic DA system. Systemic administration of the D_2/D_3 agonist quinpirole decreased sucrose (2,3) and sham sucrose intake (3). Systemically administered amphetamine increased or decreased sucrose consumption depending on the feeding conditions (food restriction vs. no restriction) of the animal (31). *d*-Amphetamine also increases responding reinforced by 10% sucrose pellets, but decreases responding for 95% sucrose pellets (25,26), and dose dependently increases or decreases daily food intake (1). Systemic administration of the DA antagonist raclopride has been shown to increase intake of high concentrations of sucrose, but decrease intake of low concentrations (25,26). More direct evidence for the involvement of the mesolimbic DA system in the intake of nondrug substances comes from the finding that intraaccumbens injections of *d*-amphetamine dose dependently increases (2.0-2.5 μg) and decreases (8.0-10.0 μg) food intake (1,8,9). Thus, the mesolimbic-mesocortical DA system may serve a general role in reinforcement processes rather than being specifically related to drug reinforcement. Because some drugs have direct action on these systems, they may have an ability to exert more control over behavior than nondrug reinforcers. However, this later hypothesis remains to be clearly demonstrated.

The present study was designed to extend our previous work with ethanol (11,12,33,34) while also examining n. accumbens involvement in reinforcement processes. The effects of intraaccumbens injections of DA agonists and antagonists were compared on responding reinforced by sucrose and sucrose/ethanol solutions. If the mesolimbic DA system plays a general regulatory role in reinforcement processes, then alterations of mesolimbic DA function should produce effects on sucrose-reinforced responding that are similar to those found with ethanol reinforced responding.

METHOD

Animals

Male Long-Evans rats (n = 33), weighing 250-300 g, were obtained from the Psychology Department's breeding facility at the University of Washington. The rats were housed individually in standard stainless steel hanging cages with food (Wayne Rodent Blox 8604, Wayne Laboratories) continuously available. Water access was restricted initially during the first 3 days of lever press shaping but was always available thereafter. The animal colony room was maintained on a 12 L : 12 D cycle with the lights on at 0700. Temperature and humidity were maintained within guidelines set by NIH (HHS pub, 1985). Experimental sessions were conducted during the light portion of the cycle.

Apparatus

The apparatus used in this study has been described previously in more detail (21,22). Briefly, operant sessions were conducted in Plexiglas chambers (27 × 37 × 21 cm) located in sound-attenuating cubicles with exhaust fans that masked external noise. Each chamber was equipped with two liquid dispensers (Ralph Gerbrands Corp., Model B-LH, Arlington, MA) that presented fluids in a 0.1 ml dipper for 3 s during each operation. Responses on a lever located on the front wall resulted in activation of the dipper located on the left wall. The right lever and dipper were inactive during the present experiment. Apple IIe microcomputers controlled experimental sessions and recorded data.

Procedure

Rats were initially housed in the colony room for 1 week to allow adaptation to individual housing conditions. During this time they were handled and weighed daily. Thereafter, they were removed from their cages daily and transported to an adjoining room for 30 min operant sessions. They were trained to lever press on a fixed-ratio (FR) 4 schedule with a sucrose or sucrose/ethanol solution presented as the reinforcer. Drinking was verified by periodic observation through a viewing window in each chamber and by measurement of the change in fluid levels in the dipper reservoirs at the end of the session.

Rats were divided into four groups. The effects of intraaccumbens microinjections of *d*-amphetamine and quinpirole were tested in three groups trained to respond with either a low sucrose (2% w/v, n = 8), high sucrose (75% w/v, n = 12), or a sucrose/ethanol mixture (sucrose 3% w/v, ethanol 10% v/v, n = 8) presented as the reinforcer. The effects of n. accumbens microinjections of raclopride were tested in a fourth group trained to respond with the high concentration sucrose (75% w/v, n = 5) reinforcer.

When response rates and patterns stabilized, cannula guides were surgically implanted in the n. accumbens. Daily operant sessions were resumed 1 week following surgery. Microinjections began when postsurgery response rates and patterns stabilized. Operant sessions were run Monday through Friday. Microinjections were conducted once per week on Thursdays with sham injections occurring each Wednesday. Sham injections were conducted each week to control for shifting baseline response totals. Data from Tuesdays were used as no injection controls.

Surgery

Rats were anesthetized with Equithesin (3.0 ml/kg IP) and placed in a stereotaxic device (David Kopf Instruments, Model 1204 with rodent adaptor) with the incisor bar 5 mm above the interaural line. Stainless steel cannula guides (26 gauge) were implanted bilaterally to terminate 1 mm dorsal to the n. accumbens. Cannulae were secured to the skull with dental cement and stainless steel cranial screws. The guide cannulae were sealed with removable obturators (33 gauge). Plastic

rings were affixed around the cannula area to prevent disruption of the obturators by grooming. The stereotaxic coordinates used for n. accumbens were 3.7 mm anterior to the bregma, 1.8 mm lateral to the midline, and 5.0 mm ventral to the cortical surface (21).

Microinjection Procedure

Prior to injections, unanesthetized animals were placed in a plastic tub (30 cm in diameter by 14 cm deep) to limit movement. Obturators were removed and the cannulae area was swabbed with sterile physiological saline. Bilateral saline and drug injections were performed through 33 gauge stainless steel tubing (glued to 26 gauge tubing) lowered to 1 mm below the end of guide cannulae. Microinjector cannulae were connected with PE-20 tubing to 1.0 μl syringes (Hamilton, Reno, NV) and mounted on a microdrive pump (Harvard Apparatus, Model 22). The pump delivered 0.5 μl/side over 60 s. Injectors remained in place for 30 additional s to allow for drug diffusion. New sterile obturators were inserted after removal of the injectors. Operant sessions began 10 min after sham and drug injections. Sham injections were identical to drug injections with the exceptions that the injectors were the same length as the guide cannulae to prevent brain penetration, and although the pump was operated, the syringes were not driven.

Drugs

The nonspecific DA agonist *d*-amphetamine sulfate (0.0, 4.0, 10.0, and 20.0 μg/μl), the D_2/D_3 agonist quinpirole (0.0, and 4.0 μg/μl), and the D_2 antagonist raclopride (0.0, 0.1, 0.5, 1.0, 3.0, and 5.0 μg/μl) were tested. All drugs were dissolved in physiological saline and shaken on a mechanical shaker. New drug solutions were prepared immediately prior to each injection session. All drugs were administered bilaterally in a total volume of 1.0 μl (0.5 μl/side).

Histology

Upon completion of the microinjection procedure, rats were deeply anesthetized with pentobarbital sodium and perfused transcardially with a sodium phosphate buffer solution (pH 7.5) followed by 10% formaldehyde. The brains were stored in 10% formaldehyde for 7 days, frozen, and then cut into 60 μm sections for cresyl violet staining. Placement of cannulae was verified using a standard light microscope (Bausch and Lomb, Galen III). Only the data resulting from bilateral n. accumbens injections were used in the analysis.

Data Analysis

Total responses. Number of ethanol-reinforced lever presses were computer recorded during each session. Data were analyzed according to a two-way repeated measures ANOVA (injection type × dose) with three levels for injection type (no injection, sham injection, and drug injection), and four levels for *d*-amphetamine dosage and five levels for raclopride dosage. Post hoc multiple comparisons were conducted using the Student-Neuman-Keuls test or paired *t*-test where appropriate.

Response pattern. Computer-generated cumulative response records were used to display the temporal distribution of responses and reinforcements. Changes in response patterns were analyzed by visually inspecting cumulative records and by quantitatively comparing drug vs. sham interresponse time (IRT) distributions as previously described (12). Briefly, the number of IRTs, up to 30 s, falling within two-second ranges (i.e., 0–2 s, 0– 4 s, . . . 28–30 s) were counted in 15 bins. IRTs greater than 30 s were counted in a 16 bin. Relative frequency distributions were then derived by dividing the number of IRTs in each bin by the total. Drug-induced changes in IRT distributions were quantified by calculating relative differences between each corresponding bin in the drug and sham distributions.

RESULTS

Histological examination of brain sections showed that the majority of injections occurred in the region of the n. accumbens. Following data exclusion due to improper cannulae placement, the *d*-amphetamine and quinpirole groups were reduced to the following number of animals: sucrose (2%), $n = 7$; sucrose (75%), $n = 10$, sucrose/ethanol (3%/10%), $n = 5$. The raclopride group (sucrose 75%) was reduced to $n = 3$. The injection sites for the rats included in the analysis are shown in Fig. 1.

Sucrose (2% w/v) Reinforcement

Responses per session. A repeated measures ANOVA showed no significant effect for dosage of *d*-amphetamine on responses per session, but the 20.0 μg dose reduced responding approximately 50% from the no injection condition ($p < 0.05$). Sham and saline control injections produced no statistically significant effect on responding compared to baseline no injection sessions (Fig. 2, top). However, injection type approached significance $F(2, 18) = 3.4$, $p = 0.06$ due to the reduction in total responses at all doses tested, including saline (Fig. 2, top). Quinpirole (4.0 μg/μl) produced a similar decrease in (mean ± SEM) number of responses per session (234.8 ± 86.5) as compared to no injection control (325.5 ± 120.9), but failed to reach statistical significance due to intersubject variability.

Response pattern. Visual inspection of cumulative records showed that sucrose (2%) reinforcement resulted in high-rate responding that continued for the duration of 30 min sessions (Fig. 3, left). *d*-Amphetamine and quinpirole typically increased initial response rate and then reduced response rate later in the session to levels below those that occurred in control conditions (Fig. 3, left). Thus, total number of responses per session were marginally affected.

Changes in response pattern were analyzed by comparing sham and drug interresponse time (IRT) distributions. The control distributions were characterized by the majority of IRTs (approximately 80%) falling between 0–6 s, indicating that most responding occurred at a high rate. Saline injections produced no relative change in the shape of the IRT distributions generated under sham conditions. Microinjections of *d*-amphetamine and quinpirole resulted in relatively little change in the number of short IRTs (2–12 s) with small relative increases distributed over the longer times which is indicative of the slowed but continuous response rate noted in the cumulative records (Fig. 3). The 20.0 μg/μl dose of *d*-amphetamine resulted in a relative increase in IRTs in the 30–32 s range with additional increases in IRTs occurring in 22–24 s range. Quinpirole (4.0 μg/μl) resulted in a similar peak shift in the 22–24 s range.

Sucrose/Ethanol Reinforcement

Responses per session. Repeated measures ANOVA revealed that the addition of ethanol (10%) to the low concen-

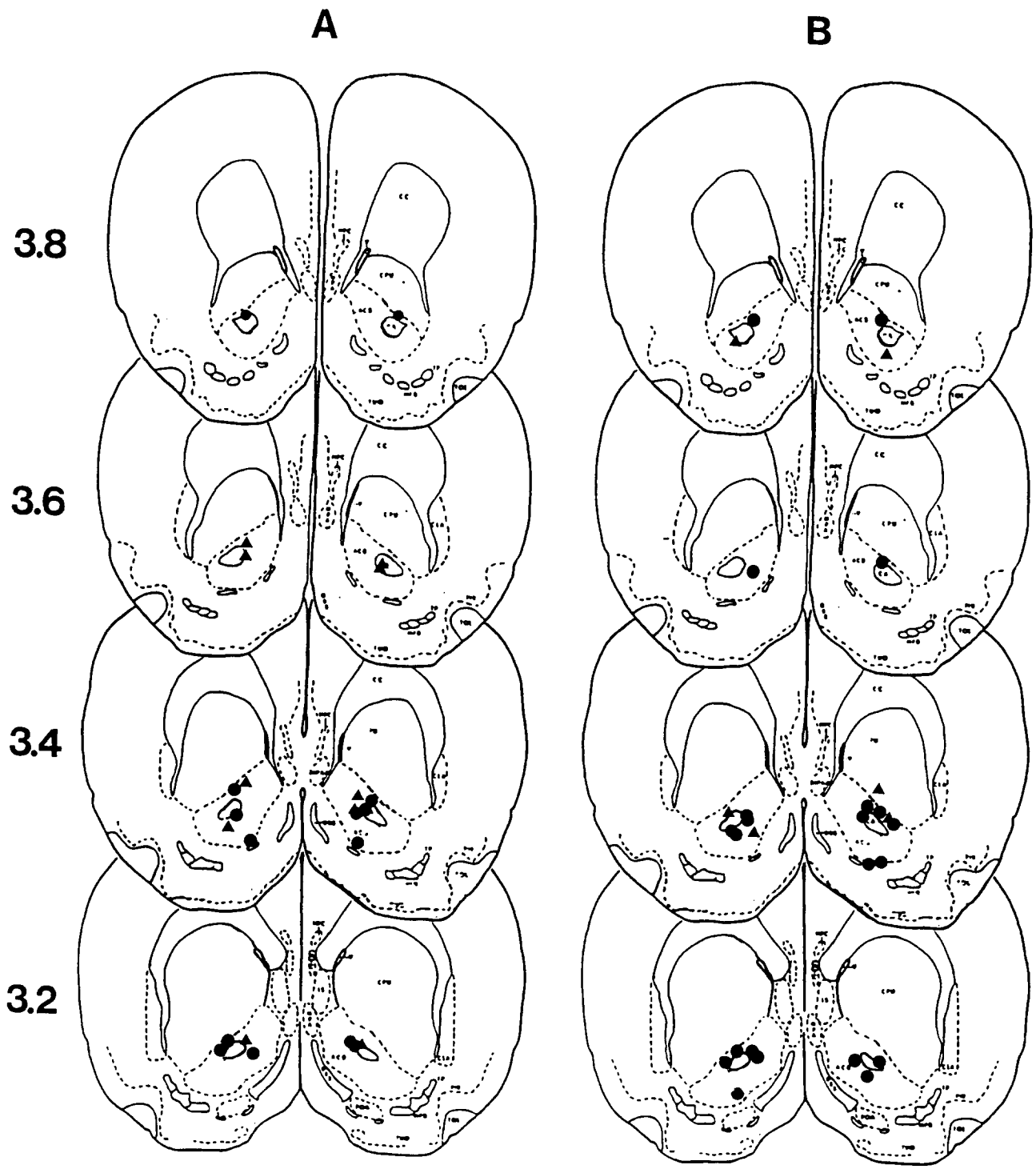

FIG. 1. Histological representations of microinjection sites within the ventral striatum (n. accumbens). Numbers on the left represent distance (mm) from bregma. Panel A shows injection sites for the 2% sucrose group (circles) and the 3% sucrose/10% ethanol groups (triangles). Panel B shows injection sites for the 75% sucrose reinforcement groups who received *d*-amphetamine and quinpirole (circles) and racloprode (triangles) injections.

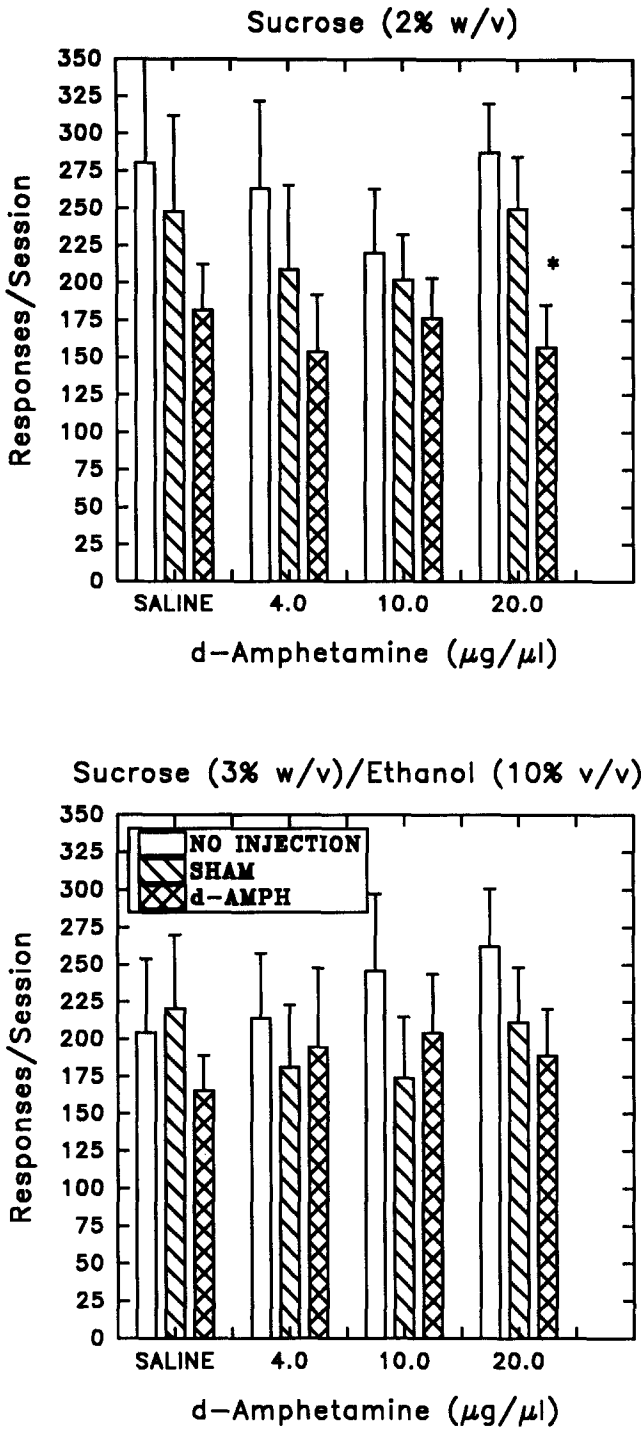

FIG. 2. Mean number of 2% sucrose (top) and sucrose/ethanol (bottom) reinforced responses per session plotted as a function of dose of *d*-amphetamine. Error bars are ± SEM. Asterisk indicates a significant from corresponding no injection control and sham injection session, $*p < 0.05$, Neuman-Keul's test.

tration sucrose solution resulted in a significant main effect for injection type, $F(2, 18) = 4.8$, $p < 0.05$, because both the sham and *d*-amphetamine injections differed from the no injection control condition, $p < 0.05$ (Fig. 2, bottom). However, there was no drug effect. Quinpirole (4.0 μg/μl) had no effect on (mean ± SEM) responses per session (207 ± 131) as compared to no injection control sessions (109 ± 11.4) because of the wide degree of variability following microinjections.

Response pattern. The response pattern with sucrose/ethanol reinforcement was characterized by initial high response rates that terminated within the first 10 min of the session. This is similar to the response pattern previously reported with ethanol (10%)-reinforced responding (11,12,33,34). *d*-Amphetamine disrupted initial high response rates shortly after onset and resulted in a slowed continuous response pattern that continued for the remainder of the 30 min sessions (Fig. 3, right). As observed with sucrose (2%)-reinforced responding, DA agonists resulted in little relative change in the shorter IRTs. *d*-Amphetamine produced an increase in IRTs between 18–20 s with an additional increase for times between 28 and 30 s. Quinpirole resulted in a peak increase at times of 12–14 s, which indicates a lower response rate than that observed with *d*-amphetamine.

Sucrose (75%) Reinforcement

Responses per session. Sucrose (75%) reinforcement resulted in total responding during control sessions that ranged from 84 to 234 responses. *d*-Amphetamine resulted in no statistically significant changes in responses per session (Fig. 4, top). Quinpirole had little effect on the (mean ± SEM) number of responses per session following the 4.0 μg/μl dose (138.6 ± 61.3) as compared to the no injection control condition (128.8 ± 64.5). However, repeated measures ANOVA showed that raclopride resulted in a significant dose effect, $F(5, 10) = 5.7$, $p = 0.009$, and a significant injection × dose interaction, $F(10, 20) = 2.5$, $p < 0.05$, (Fig. 4, bottom). Post hoc multiple comparisons showed that the main effect for dose and the injection × dose interaction were due to significant decreases in responses per session at the 1.0, 3.0, and 5.0 μg/μl doses of raclopride as compared to saline control ($p < 0.05$). Individual comparisons showed that response totals following the 3.0 and 5.0 μg/μl doses were significantly lower than those following the 0.5 μg/μl dosage of raclopride ($p < 0.05$).

Response pattern. Visual inspection of cumulative records showed that sucrose (75%) reinforcement resulted in response patterns more similar to those previously reported with ethanol reinforcement (11,12,33,34) than did the sucrose (2%) reinforcement. Microinjections of *d*-amphetamine and quinpirole typically produced a shift in pattern to a slow response rate that continued for the total session (Fig. 5, left). The effects of raclopride on response pattern was similar to those found when responding is reinforced by ethanol (Fig. 5, right). That is, the initial high response rate was unaffected by the low doses of raclopride, but responding terminated earlier. Higher doses of raclopride delayed the onset of responding, produced slower rates after onset, and terminated responding shortly after onset (Fig. 5, right).

The DA agonists slowed response rates by increasing the relative proportion of longer IRTs, which is indicative of the slow continuous pattern. Quinpirole produced a peak increase in IRTs in the 20–22 s time bin, whereas *d*-amphetamine produced a peak increase in the 14–16 s time bin. This indicates that both drugs resulted in a slowed continuous response rate, but rates following *d*-amphetamine were higher than those following quinpirole injections. Raclopride resulted in less disruption of local response rates and did not produce a peak increase in any time bin.

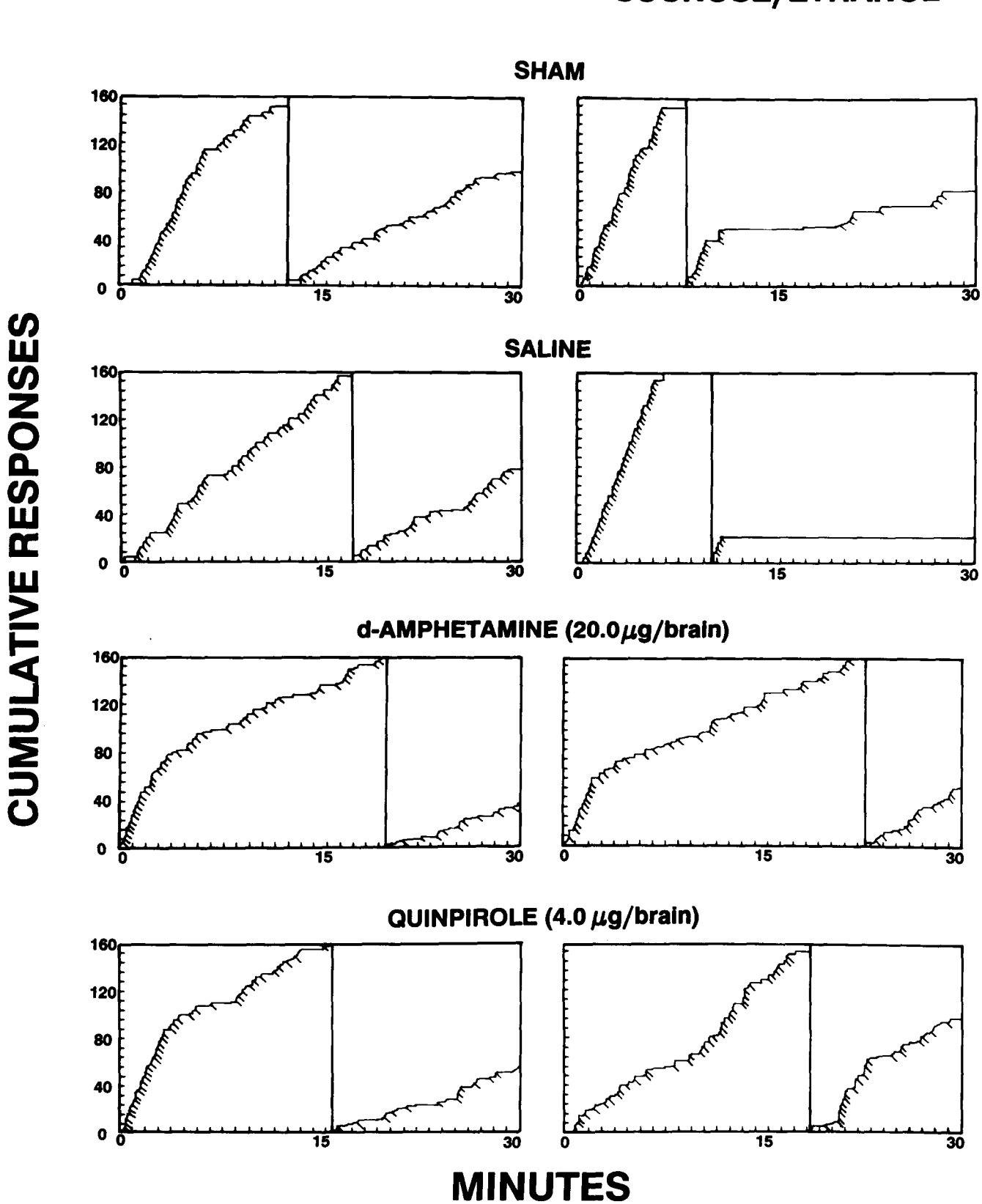

FIG. 3. Representative computer generated cumulative response records for 2% sucrose (left) and sucrose/ethanol (right) reinforcement plotted as a function of session duration to show response pattern. Diagonal pips on the graphs indicate delivery of 0.1 ml of the reinforcer. The slope of the line indicates response rate (responses/min).

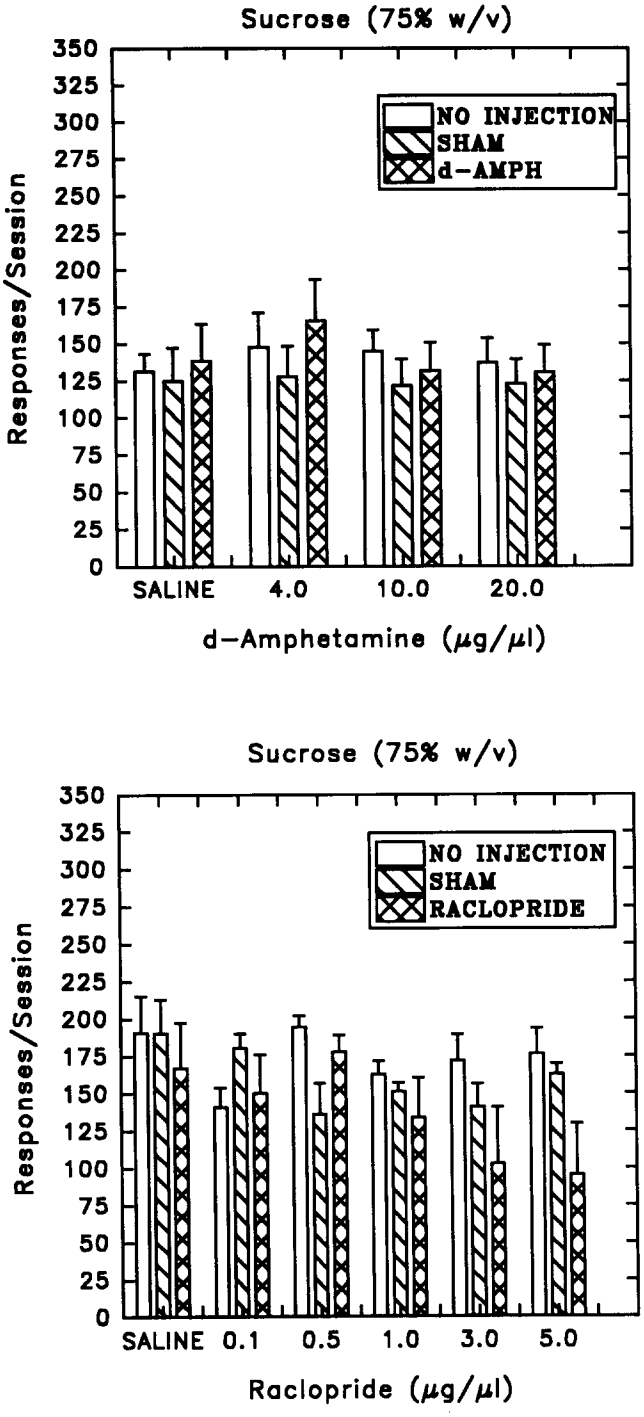

FIG. 4. Mean number of 75% sucrose reinforced responses per session plotted as a function of dose of *d*-amphetamine (top) and raclopride (bottom). Error bars are ± SEM.

DISCUSSION

Animals self-administering ethanol in an operant situation increase their total session responding following microinjections of the mixed DA agonist *d*-amphetamine into the n. accumbens (12,32-34). The increase is due to a shift in response pattern from high response rate with early offset to a slower rate that continues for as long as 1 h (12). Altering n. accumbens DA transmission either through local injection of the D_2 antagonist raclopride (33) or ventral tegmental injections of the D_2 agonist quinpirole (11) decreases ethanol reinforced responding by delaying onset and then terminating responding shortly after onset. The purpose of the present experiment was to test the effects of intraaccumbens injections of DA agonists and antagonists on responding reinforced by sucrose and sucrose/ethanol solutions to further clarify the manner and specificity by which the mesolimbic DA system regulates ethanol reinforced behavior.

When 2% sucrose was presented as the reinforcer, baseline response patterns were characterized by moderate to high response rates that continued for the duration of 30 min operant sessions. Microinjections of *d*-amphetamine 20.0 μg/μl of *d*-amphetamine produced a biphasic effect on the response pattern. In the initial period of sessions, response rate was mostly increased, followed by a slowing of response rate that was sufficient to significantly decrease number of responses per session. Quinpirole (4.0 μg/μl) produced a similar effect on response rate but failed to significantly decrease the total number of responses. The decrease in responding is similar to other findings showing decreases in food intake at higher doses (8.0 and 10.0 μg) of intraaccumbens *d*-amphetamine (1,8,9). Although the present experiment showed decreases in sucrose (2%) reinforced responding, it should not be concluded that *d*-amphetamine-induced increases in n. accumbens DA levels always result in this effect. Other studies using nonoperant tasks have shown increases in food intake at lower *d*-amphetamine doses (2.0 and 2.5 μg) than those tested in the present study (1,8,9).

Previous research with ethanol (10%) reinforcement suggests that differential effects of *d*-amphetamine may be due to the reinforcer or the baseline pattern of responding generated under different reinforcement conditions. Unlike 2% sucrose, ethanol reinforcement results in biphasic baseline response patterns characterized by a high response rate early in 30 min operant sessions that terminates after approximately 10 min (11,12,33,34). Microinjections of a high dose of *d*-amphetamine (20.0 μg/μl) increased the number of ethanol reinforced responses per session by slowing the initial rate and increasing response rate later in the session (12,33,34). This rate-dependent effect of *d*-amphetamine has been demonstrated on a wide range of behavioral procedures such as locomotor activity, avoidance, and different reinforcement schedules [see (4) for a review]. Thus, the failure to find an increase in responding for the low concentration sucrose used here may have been due to the different reinforcer or the high baseline response rate.

Therefore, sucrose (75%) and the ethanol/sucrose mixture were used as reinforcers in an attempt to more closely approximate baseline response rate and pattern generated by 10% ethanol reinforcement (11,33). A post hoc Kruskal-Wallis one-way ANOVA on ranks showed a significant difference among response totals during no injection control sessions, $H(1, 2) = 7.6$, $p = 0.02$, that was due to a difference between the 2% and 75% sucrose groups, ($p < 0.05$). The sucrose/ethanol and 75% sucrose groups did not differ. This corresponds with previous data indicating that baseline response pattern and rate with 10% ethanol or 75% sucrose reinforcement did not differ (11). Additionally, visual inspection of cumulative records showed that response pattern in both the sucrose/ethanol and 75% sucrose groups resembled those generated by 10% ethanol reinforcement (11,33). That is, response pat-

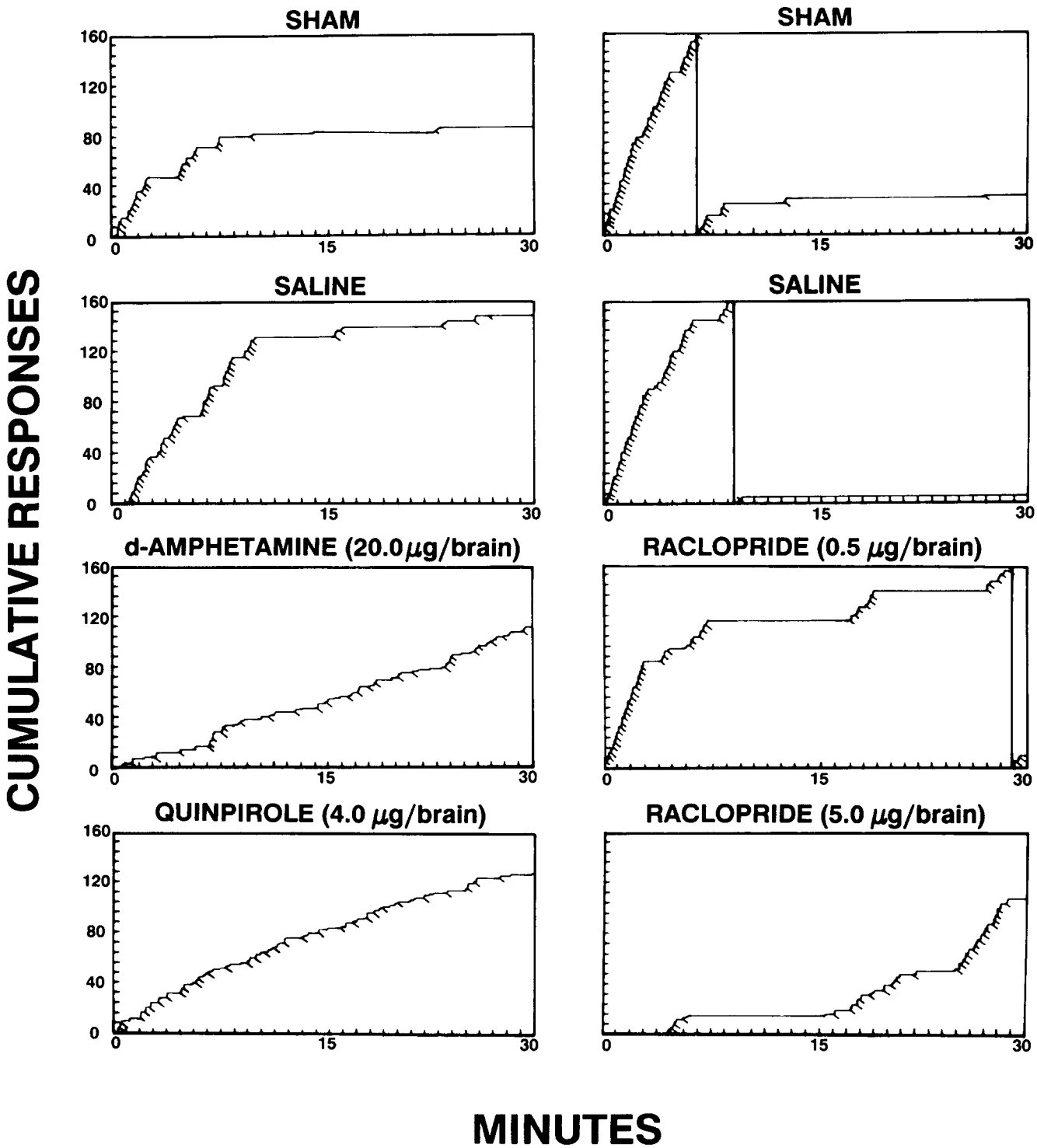

FIG. 5. Representative control and drug injection session computer generated cumulative response records for 75% sucrose reinforcement following *d*-amphetamine and quinpirole (left) and raclopride (right) injections plotted as a function of session duration to show response pattern. Diagonal pips on the graphs indicate delivery of 0.1 ml of the reinforcer. The slope of the line indicates response rate (responses/min).

tern was mostly characterized by an initial high rate that terminated during the first 10 min of the session.

In the current experiment, intraaccumbens injections of the DA agonists altered the initial high response rate early in the session and produced a steady but slowed response rate thereafter (Fig. 5), an effect that resembles our previously reported finding with ethanol reinforcement following n. accumbens injections of *d*-amphetamine and quinpirole (12,33). However, with ethanol reinforcement, the changes in response pattern resulted in significant increases in the number of responses per session (33,34). No increases in number of responses per session occurred in the present study with either 75% sucrose or sucrose-ethanol reinforcement, suggesting that mesolimbic DA mechanisms involved in ethanol and sucrose reinforcement may share processes but are not identical. It is also possible, although baseline response rates and patterns appeared equivalent across the different reinforcers, that there exists a qualitative difference among sucrose, sucrose-ethanol, and ethanol reinforcement that alters the manner in which the mesolimbic DA system influences responding. Further studies using concurrent presentation of sucrose and ethanol reinforcement, or different concentrations of ethanol and sucrose reinforcement, will be necessary to more completely characterize the relation between behavioral response pattern, reinforcer type, and mesolimbic DA involvement.

Additional evidence suggesting similar but not identical mesolimbic DA mechanisms in ethanol and sucrose reinforcement comes from the present finding that raclopride injections in n. accumbens decreased 75% sucrose reinforced responding in a manner similar to that previously reported with 10% ethanol (33). The effect of raclopride with both reinforcers is to delay the onset of responding and terminate the normal high rate shortly thereafter. However, with 75% sucrose reinforcement, in two of the three rats tested in the present study, responding resumed after a pause of approximately 10 min from the first termination (Fig. 5). Resumption of responding after raclopride-induced early offset has not been observed with ethanol reinforcement (33,34). Additionally, the dosage of raclopride required to disrupt sucrose reinforced responding was 10 times greater than that required to significantly reduce ethanol reinforced lever pressing (33). This rightward shift in the dose-response curve corresponds to a similar finding comparing ethanol and sucrose reinforced responding following ventral tegmental injections of quinpirole (11).

Systemic administration of raclopride has been shown to increase lever pressing for 34% sucrose pellets (20,26) and 95% sucrose pellets (25), but not for lower concentrations of sucrose (25,26). In contrast, the present data show that n. accumbens injections of raclopride (0.1–5.0 $\mu g/\mu l$) decreased responding for 75% sucrose. A possible explanation for the opposite results produced by systemic and n. accumbens administration of raclopride is that systemic administration of raclopride effects additional DA systems, such as the nigrostiatal DA system, which may engage additional motor and/or motivational processes (16,19). However, reinforcer type may also alter the effects of raclopride.

Understanding the neuropharmacological aspects of alcohol abuse will involve elucidation of the specific effects that manipulation of the mesolimbic-mesocortical DA systems may have upon self-administration behavior. Data from previous studies indicated that microinjecting DA agonists and antagonists, in n. accumbens, increased or decreased ethanol reinforced responding, respectively (12,33,34). This suggests that ethanol self-administration, like that of other drugs of abuse, is partly controlled through this system. The present studies demonstrate that the effects seen on ethanol reinforced behavior are similar, to some degree, to those observed on behavior reinforced by "natural" reinforcers, such as sucrose, when baseline response patterns are equated. However, there do appear to be differences in the nature of mesolimbic DA control over ethanol and sucrose reinforced responding that may suggest a specific role for this system in the regulation of ethanol self-administration.

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