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Oral Ethanol Self-Administration in the Rat: Effect of Naloxone

HERMAN H. SAMSON[1] AND TERESA F. DOYLE

Department of Psychology and Alcohol and Drug Abuse Institute, University of Washington, Seattle, WA

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SAMSON, H H AND T F DOYLE *Oral ethanol self-administration in the rat Effect of naloxone* PHARMACOL BIOCHEM BEHAV 22(1) 91–99, 1985 —Rats responding on a two lever concurrent for ethanol and water, were injected with 5, 10, or 20 mg/kg naloxone hydrochloride 30 min prior to a 30 min session Only the 20 mg/kg dose had any effect, a decrease in responding for ethanol of up to 50% compared to saline control injection sessions There were no systematic effects upon water responding An additional study using sucrose and water as the fluid concurrently available failed to find any effects of naloxone on sucrose responding at the same doses The effect upon ethanol responding was found not to resemble a pattern of extinction, but rather was best described as a general overall reduction in responding. The relation of these findings to the direct involvement of the endogenous opiate system in ethanol reinforcement is discussed

Ethanol Self-administration Naloxone Endogenous opiates Rats

A variety of studies has shown that animals will work to obtain access to ethanol solutions [2, 33, 46, 56]. Intravenous (IV), intragastric (IG) and oral self-administration of ethanol have been examined using a variety of preparations and species As a result of these investigations, it has been suggested that ethanol maintained behavior is similar to self-administration of other drug classes [15]

One research area of major concern for the understanding of drug maintained behavior is the determination of the underlying physiological systems involved [3, 14, 49, 54, 55] Many neuroanatomical and neurochemical systems have been shown to be affected by ethanol exposure (e.g., [12,50]). During the last several years, the possible interaction of the endogenous opiate system with ethanol and its metabolites has received a great deal of attention [5, 9, 36]. While various effects of ethanol on the endogenous opiate system have been demonstrated [19, 20, 38, 45, 51], and opiate antagonists have been found to alter ethanol's effects under some conditions [23, 24, 35, 37], little work has been done on the interaction of opiate antagonists and ethanol self-administration

In a study of IV ethanol self-administration in the monkey, Altshuler *et al* [1] found that chronic treatment on a daily basis for 15 days with naltrexone decreased the daily ethanol self-administration by as much as 50% From this study, the authors concluded that the reinforcing properties of ethanol maintaining the self-administration behavior might be functioning via the endogenous opiate system. These authors [1] suggest that the opiate antagonistic effects of naltrexone blocked ethanol reinforcement resulting in the observed decrease in ethanol self-administration. While these results could suggest that the endogenous opiate system might be directly involved in IV ethanol self-administration, the involvement of this system with oral ethanol self-administration remains to be demonstrated. In addition, the use of a chronic dosing procedure [1] with narcotic antagonists makes the direct role of the endogenous opiate system unclear, as this procedure has been shown to lead to a variety of sensitization effects which could account for the decreased ethanol self-administration [34, 47, 52, 58]. To examine the role of the endogenous opiate system in ethanol reinforcement, the following experiment was performed using acute naloxone pretreatment in rats orally self-administering ethanol

EXPERIMENT 1

METHOD

Animals

Eight male Long-Evans rats (90 days old), whose free-feeding weights ranged from 310 to 410 g, were used. They were obtained from the breeding facility of the Department of Psychology of the University of Washington and were individually housed in standard hanging cages in a multiple cage rack system Artificial lighting was regulated on a 12 hr light/12 hr dark cycle (on at 07:00 hr) Water was available at all times in the home cage except as specified below Food was rationed daily to maintain the animals throughout the experiment at 80% of their free-feeding weights. On Monday through Friday, the daily food rations were given immediately following the 1/2-hr operant session, except as noted below. Experimental sessions were run five days per week, Monday through Friday, during the first half of the light cycle.

[1]Requests for reprints should be addressed to Herman H Samson, Department of Psychology, NI-25, University of Washington, Seattle, WA 98195

Apparatus

The operant chambers and their enclosures have been described in detail previously [39]. Briefly, each chamber had two levers and two liquid dipper dispensers (Ralph Gebrands Corp., Model No. B-LH, Arlington, MA) mounted on the front wall. Responses on the right lever resulted in presentation of the dipper to the right of that lever, and responses on the left lever resulted in presentation of the dipper to the left of that lever. All dipper operations provided 3-sec access to the 0.1-ml dipper. During a session a small lamp (1 W) illuminated each chamber. An exhaust fan provided air circulation for the operant chamber, which was housed inside a sound attenuating outer chamber. Schedule control and data acquisition were with an Apple microcomputer.

Drugs

Naloxone hydrochloride (Endo Labs Inc. Wilmington, DL) was weighed out prior to each weekly injection day and dissolved in 0.9% sterile saline. A new drug solution was prepared each week. Depending on the dose to be administered, either 5, 10 or 20 mg/ml concentrations were prepared. Sterile, isotonic saline was used for the control injections.

Procedure

Following reduction to 80% of their free-feeding weights, each animal received a single daily session in the operant chamber. Initially, the sessions were 15 minutes long. The animals were placed on a 23-hr water deprivation regimen and trained to press the left lever to obtain access to water presented in the left dipper. During shaping of the response on the left lever, the right lever was removed from the chamber. Following the session, the animal was fed its daily food ration and given 1-hr access to water in the home cage.

When responding was well established on a continuous reinforcement schedule, the animals were placed on a fixed ratio two (FR 2) schedule. The schedule requirements were then increased gradually over sessions until stable responding at FR 8 was attained. Next, the left lever was removed, the right lever inserted, and FR responding shaped on the right lever using the same procedure. When stable FR 8 responding for water occurred on the right lever, the left lever was reintroduced and a concurrent FR 8 FR 8 schedule with water available at both dippers instituted. To insure that lever independence was maintained, a 3-sec changeover delay was in effect at all times during the concurrent schedule.

After obtaining stable responding on the FR 8 FR 8 concurrent with water presented in both dippers, the procedure previously used in our laboratory to establish ethanol maintained responding was begun [38, 39, 40]. At this time, sessions were increased in length to 30 minutes. Ethanol (5% v/v) was placed in one dipper reservoir, with water remaining in the other. The FR 8 FR 8 concurrent schedule was not changed. In this phase of the experiment, 5 g of the daily food ration was placed into the operant chamber at the start of each session. Also, the water-deprivation regimen was discontinued at this time and ad lib water was available on the home cage. The dipper locations of the ethanol and water were alternated each session. If needed, some behavioral manipulations (e.g., an FR increase or removal of the preferred lever) were used to correct for lever preferences that had developed during the water-water concurrent condition.

TABLE 1

BASELINE RESPONDING FOR ETHANOL AND WATER (MEANS ± S.D.)

	Responses			
Animal	Ethanol	Water	Ethanol/Total × 100	Ethanol Intake
N5	565 (47)	30 (12)	95	0.96
N7	132 (23)	89 (7)	59	0.22
N8	452 (46)	65 (9)	87	0.68
N40	408 (66)	106 (17)	78	0.78
N41	368 (31)	56 (6)	87	0.73
N42	446 (94)	135 (47)	80	0.84
N43	366 (29)	125 (10)	74	0.77

Ethanol intakes are in g ethanol/kg body weight

Once preferential responding for ethanol was established, as determined by a majority of daily responding predominantly occurring on the lever associated with ethanol presentation, the total daily food ration was placed in the home cage following the session.

When stable ethanol maintained responding was established, intraperitoneal administration of saline or naloxone was initiated. All injections were administered 1/2 hour prior to the start of the 30 min session. Weekly injection schedules were as follows: Monday, no injection, Tuesday, saline, Wednesday, saline or naloxone, Thursday, saline, Friday, no injection. The first week of injections consisted of saline administrations only. This was done to determine both the effects of injection on responding, and to accustom the animals to the injection procedure. In succeeding weeks, naloxone was administered prior to the Wednesday session, with saline injected on the days immediately preceding and following. Only one drug dose was tested each week. Three doses of naloxone were tested: 5 mg/kg, 10 mg/kg and 20 mg/kg, administered in an ascending order. Every animal received each dose at least twice. Number of lever presses, dipper operations, changes in fluid reservoir levels and cumulative response records were recorded for each daily session.

RESULTS

Of the eight animals starting the study, one (rat N6) became ill with a respiratory problem and was removed during the early phases of the experiment. The data from this animal are not included in the analyses. Table 1 presents the baseline data for the remaining 7 rats taken from the week prior to beginning injections. Six of the rats showed strong preferential responding for ethanol as shown in both the number of responses for ethanol and the % of total responding on the ethanol lever. These data are very similar to previous data from our laboratory using the same procedure to initiate ethanol maintained behavior [38, 39, 40]. Of the six rats that did show strong ethanol responding, five followed ethanol as it changed lever positions across sessions. One animal demonstrated a marked lever preference (rat N42) such that on days in which ethanol was on the nonpreferred lever, responding was about one half of that observed when ethanol was on the preferred lever. Another rat (rat

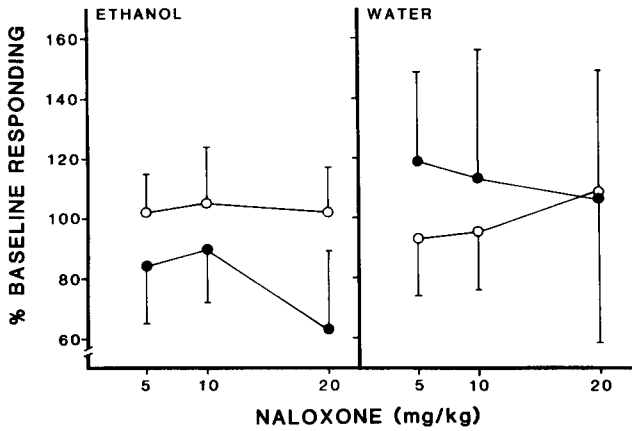

FIG 1 Change from baseline responding (means and sd) for ethanol and water on saline (open circles) and naloxone (closed circles) injection days

N7) developed a very strong lever preference and would make few responses on the other lever, independent of the fluid being presented with the preferred lever. Except at the very end of the experiment, this last rat failed to develop the response pattern generally used in our laboratory to indicate that ethanol is maintaining behavior [39,40]. While this animal's data have been included in the general analysis, a separate analysis without the animal's data was performed It was determined from this second analysis that the inclusion of the data from this rat did not change the overall outcome of the experiment in any way

The mean (±SD) percent of baseline responding (non-injection days of the same week compared to injection days) for saline injections and naloxone injections for both ethanol and water at each naloxone dose is presented in Fig. 1 An analysis of variance (lever(2) × condition (no injection, saline, naloxone (3)) × repeated measures within subjects design) using individual session responding at each naloxone dose was performed independently for ethanol and water (Table 2) No significant differences at the 5 mg and 10 mg dose levels were found, but a significant difference for treatment conditions was found at the 20 mg dose, $F(2,12)=15.217$, $p<0.01$. Post hoc comparisons found that responding on naloxone days was significantly different from both non-injection baseline days, $F(1,13)=17\ 517$, $p<0.01$, and saline injection days, $F(1,13)=14.874$, $p<0.01$. There were no significant effects dependent upon lever or drug presentation order at any naloxone dose tested The same analysis of variance on water responding was significant at the 5 mg dose, $F(2,12)=11\ 457$, $p<0\ 01$ Post hoc analysis found that on naloxone injection days, water responding was significantly increased compared to both no injection days, $F(1,13)=10\ 904$, $p<0\ 01$, and saline injection days, $F(1,13)=8\ 587$, $p<0\ 05$ No other significant effects on responding were found at any other dose nor were there any lever or drug-order effects

Figure 2 presents representative cumulative records of ethanol responding for each dose of naloxone Neither the 5 mg or 10 mg dose had any effects upon responding when compared to the saline control records. Both response rates and pattern of responding were unaffected at these doses, as suggested by the above statistical analyses. At the 20 mg dose, rate of responding was clearly decreased, resulting in

TABLE 2

ETHANOL AND WATER RESPONSES (MEAN) FOR ALL CONDITIONS AT EACH NALOXONE DOSE

	Ethanol			Water		
Animal	NI	SAL	NAL	NI	SAL	NAL
5 mg/kg						
N5	507	480	420	26	28	36
N7	82	92	86	78	72	88
N8	404	417	372	60	46	75
40	425	431	336	98	75	97
41	276	263	250	69	68	88
42	412	378	266	129	113	182
43	257	263	192	114	98	124
10 mg/kg						
N5	501	514	396	34	36	56
N7	147	176	135	94	100	70
N8	489	517	385	67	54	99
40	408	410	386	96	94	80
41	335	366	408	60	48	50
42	434	376	365	146	160	114
43	348	382	320	164	130	116
20 mg/kg						
N5	583	582	225	32	24	22
N7	158	170	86	104	90	50
N8	452	529	365	70	56	102
40	446	446	308	112	96	102
41	444	450	417	54	61	58
42	560	553	285	115	150	139
43	428	396	144	120	110	106

NI=no injection baseline
SAL=saline injection days
NAL=naloxone injection days

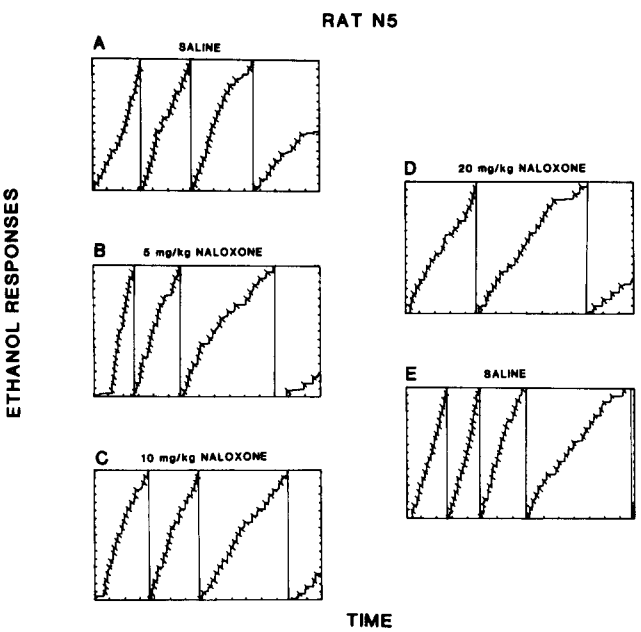

FIG 2 Representative cumulative records for effects of naloxone at each dose tested on ethanol responding (Rat N5, Grids=5 responses/division 2 min/division)

the observed decrease in total responding It should be pointed out that these rate decreases were observed throughout the session, and did not develop over the session At no time was a response pattern observed indicative of an extinction process resulting from removal of reinforcement (see [13] for the general extinction responding patterns expected) In some sessions, no effects on responding at the 20 mg/kg dose were seen. At other times, and at all doses tested, increased water responding produced breaks in ethanol responding, which sometimes resulted in decreased total ethanol responding

DISCUSSION

The results indicate that a high dose of naloxone can affect ethanol responding, resulting in a decrease in oral ethanol self-administration However, at the higher naloxone dose used in this study, suppressive effects on a variety of behaviors have been noted [4, 7, 17, 21, 31, 43] Thus, the reduced ethanol responding may be due to nonspecific antagonist effects at the high dose [44]. Since antagonist doses of 5 mg/kg and lower have been shown to be effective in blocking the effects of morphine in the rat [10, 11, 25, 28, 32, 53], it would seem possible that the reduced ethanol responding observed only at the 20 mg/kg naloxone dose was due to non-specific effects of naloxone, and not the result of specific opiate receptor blockade which reduced the reinforcing capability of ethanol This indirect, non-specific hypothesis is supported by the failure to find a typical extinction pattern on responding for ethanol at any naloxone dose tested To further examine the possibility of a non-specific action of naloxone on responding, Experiment 2 was performed

EXPERIMENT 2

Prior work in our laboratory [41] had determined that when ethanol was paired concurrently with a 1% sucrose (w/v) solution, approximately equal amounts of responding resulted for both ethanol and sucrose Therefore, one control for the non-specific effects of naloxone would be the use of a 1% sucrose-water concurrent schedule situation, which should equate sucrose responding to the ethanol response patterns observed in Experiment 1 An initial attempt to train animals to respond for 1% sucrose employing the induction procedure used to initiate ethanol responding in Experiment 1 was unsuccessful Stable baseline responding could not be maintained nor would the animals follow the 1% sucrose as it alternated positions across sessions Response patterns observed for higher sucrose concentrations (e g , 3%) were found not to be comparable to the ethanol responding in Experiment 1 Because of this failure to induce 1% sucrose-maintained responding, the following experiment used a different initial induction procedure

METHOD

Animals

Eight, male Long-Evans rats (90 days old), obtained and housed as in Experiment 1, were used Their free-feeding body weights ranged from 350 to 470 g As in Experiment 1, the animals were gradually reduced to 80% of their free-feeding weights by food restriction and these weight levels were maintained throughout the experiment Water was available at all times on the home cage

TABLE 3

BASELINE RESPONDING FOR SUCROSE AND WATER (MEANS ± S D)

	Responses		
Animal	Sucrose	Water	Sucrose/Total × 100
N19	543 (102)	58 (21)	90
N20	354 (142)	60 (28)	86
N21	564 (266)	31 (12)	95
N22	855 (216)	30 (19)	97
N23	1346 (36)	12 (4)	99
N24	643 (140)	54 (14)	92
N25	358 (173)	14 (11)	97

Apparatus and Drugs

The identical apparatus and drug preparation as in Experiment 1 were used

Procedure

Following weight reduction, the animals were shaped to lever press to receive dipper presentations of 20% sucrose on a continuous reinforcement schedule The schedule requirements were gradually increased over sessions to FR 8 and after obtaining stable responding on each lever individually, a water-20% sucrose FR 8 FR 8 concurrent condition was instituted At this time, the operant sessions were lengthened from 15 to 30 minutes When the animals had demonstrated a sucrose preference (alternating levers across sessions so as to follow the lever associated with the sucrose solution), the concentration of sucrose was gradually reduced to 1% (starting at 20%, the concentrations used were 10, 5, 4, 3, 2 and then 1% sucrose (w/v) over 30 sessions Once stable responding was established at the 1% sucrose concentration with the animal making the majority of responses on the lever associated with sucrose, the injection procedure was begun

The schedule of injections of saline and naloxone was identical to that used in Experiment 1 The same three doses of naloxone were tested 5 mg/kg, 10 mg/kg, and 20 mg/kg Only one dose was tested each week, and each animal received every dose twice Drug doses were given in an ascending order All injections were administered 1/2 hour prior to the operant session

RESULTS

The data from seven animals were used in the analysis of the study, as one animal ceased to respond in the operant chamber before receiving all doses of naloxone and was removed from the experiment All animals displayed strong preferential responding for 1% sucrose and followed it as it alternated levers across sessions (Table 3)

An analysis of variance (same design as used in Experiment 1) at each dose level, comparing responding on no injection days, saline injection days and naloxone injection

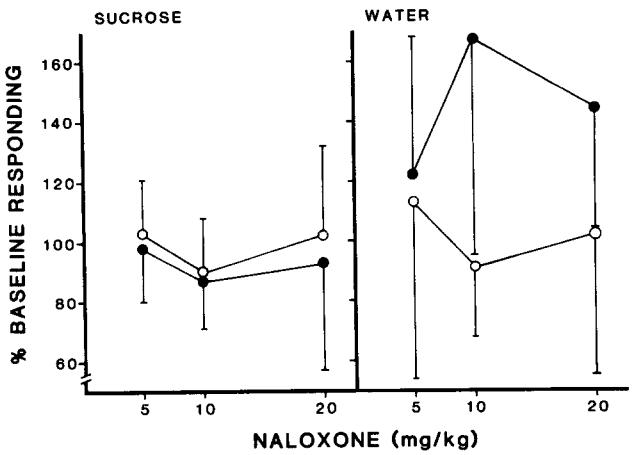

FIG 3 Changes from baseline responding (means and sd) for sucrose and water on saline (open circles) and naloxone (closed circles) injection days

days found no significant effects on sucrose responding (Fig 3, Table 4). It was noted that responding was decreased in two animals (N21 and N22) at the 20 mg/kg dose, but responding was not significantly changed in the other animals at this dose (Table 4)

An analysis of variance at each drug dose on water responding was not significant at the 5 mg/kg and 10 mg/kg doses. At the 20 mg dose, a small but significant difference between injection conditions was found, $F(2,12)=4.61, p<0.05$ (Fig. 3). A post hoc analysis found that a significant increase in responding for water occurred on naloxone days when compared to either baseline responding (t for correlated means $(1,12)=2.1287$, $p<0$ 05, or saline injection days, (t correlated means $(1,12)=2$ 1246, $p<0.05$, at the 20 mg/kg dose There was no signficiant difference at the 20 mg dose between baseline and saline injection days for water responding It should be noted that absolute water responding was low, such that, in some instances, an additional 8 responses (i.e., a single reinforcement) represented a 50% increase in responding over baseline (Table 4).

Figure 4 presents typical cumulative records of sucrose responding for each dose of naloxone (rat N20). As indicated by the statistical analysis, neither response rate nor total responses were affected by naloxone at any dose

DISCUSSION

The results indicate that naloxone, at the doses tested, did not affect sucrose or water responding. It is possible that an even higher naloxone dose might have resulted in a statistically significant decrease of sucrose responding. However, other investigators, in different experimental situations, have reported suppression of sucrose intake by naloxone at the doses used in this study [42, 48, 57] Sanger and McCarthy [43] found a significant response decrease with naloxone (10 mg/kg and 30 mg/kg dose using a FR 20) in rats lever-pressing for sweetened milk, which suggests that under certain operant conditions, naloxone can affect responding for a sweet solution One difference between the present studies and many of those cited above was the use of food deprivation, which has been shown to alter the effectiveness of naloxone on ingestive behaviors under some conditions [42].

TABLE 4

SUCROSE AND WATER RESPONSES (MEAN) FOR ALL CONDITIONS AT EACH NALOXONE DOSE

	Sucrose			Water		
Animal	NI	SAL	NAL	NI	SAL	NAL
5 mg/kg						
N19	532	672	496	30	46	60
N20	344	310	340	41	38	27
N21	377	384	356	18	15	20
N22	956	1024	704*	25	25	31*
N23	923	932	807	8	4	10
N24	487	442	442	38	34	31
N25	304	304	384	11	18	35
10 mg/kg						
N19	779	631	732	39	36	24
N20	281	282	186	41	40	80
N21	393	246	361	16	12	36
N22	862	880	724	27	22	20
N23	892	894	740	4	6	10
N24	752	621	644	31	31	32
N25	324	317	354	9	8	22
20 mg/kg						
N19	729	634	634	32	37	72
N20	364	316	302	38	38	61
N21	414	322*	252	24	25*	19
N22	754	886	560	62	54	104
N23	833	840	764	8	6	8
N24	600	610	710	40	37	42
N25	348	344	428	10	12	18

NI=no injection baseline
SAL=saline injection days
NAL=naloxone injection days
*Data for one injection only

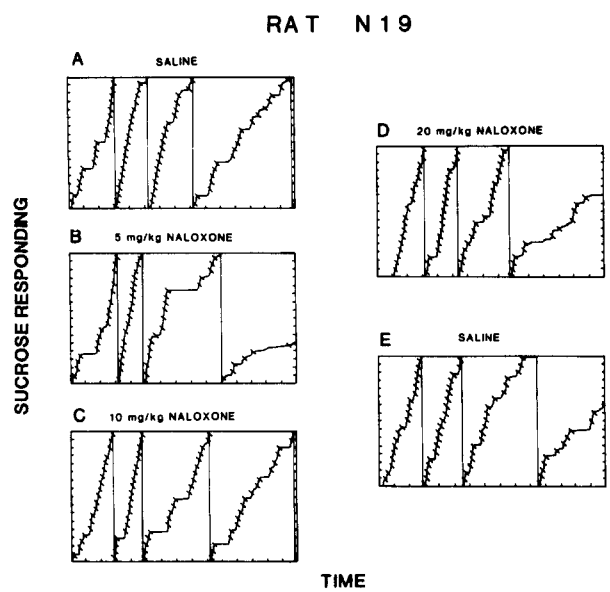

FIG 4 Representative cumulative records for the effects of naloxone on sucrose responding (Rat N19, Grids=5 responses/division 2 min/division)

It is of interest that the 1% sucrose solution failed to maintain stable responding when initially introduced with the same procedure used to establish ethanol maintained responding This 1% sucrose concentration, when paired with ethanol in a concurrent situation after ethanol is maintaining behavior, will maintain stable, moderate response levels comparable to the ongoing, ethanol-maintained lever pressing [41] As shown in Experiment 2, strong behavioral maintenance with this sucrose concentration can occur when introduced using a decreasing concentration procedure The failure of this sucrose solution to maintain behavior when used in place of ethanol in the induction procedure used in Experiment 1 is of major theoretical interest to the understanding of how ethanol maintained behavior becomes established Only further research will be able to determine what variables are important regarding this difference observed between 1% sucrose and 5% ethanol

GENERAL DISCUSSION

The present studies suggest that a high dose of naloxone (20 mg/kg) can decrease ethanol self-administration while not affecting another ingestive behavior It could be concluded, therefore, that oral ethanol reinforcement is the result of specific action via the brain endogenous opiate system, either through direct activation of this system by ethanol itself or by a metabolic product of ethanol which then activates the opiate receptors (i.e , a TIQ) However, several points should be considered before accepting this hypothesis

As discussed above, much lower doses of naloxone have been shown to be effective in blocking opiate effects in the rat [10, 11, 25, 28, 53] If an ethanol-opiate receptor interaction did result from the pattern of oral self-administration observed in Experiment 1, two results would be expected First, at least 5–10 minutes of drinking should be needed before any receptor activity could occur (i e , given the rate and quantity of oral ethanol intake, the minimal time needed to produce blood or brain ethanol and metabolic breakdown products that could have direct opiate receptor interaction would be at least 5 min) Thus, no effect of naloxone should be evident early in the session Second, given that the total ethanol intakes observed in this study produce blood ethanol levels around 50 mg/dl by the end of the session, one would predict that, at best, small amounts of specific opiate receptor agonists could be formed (i e , there should be few, if any, metabolic products formed given the levels of ethanol in the system) Thus, it would be hypothesized that the amount of opiate antagonist needed to counter the reinforcing properties of ethanol via the endogenous opiate system should be at or below the dose needed to antagonize morphine However, the present data indicate that only very high antagonist doses (approximately 40 times that required to antagonize morphine) affected ethanol responding, and when ethanol responding was reduced, it was from the beginning of the session These two factors make it difficult to accept the hypothesis that the mechanism for maintaining ethanol responding was via specific action of ethanol or its metabolic breakdown products on the endogenous opiate system An alternative hypothesis, more parsimonious with the results, suggests that rather than direct involvement, an indirect interaction of the endogenous opiate system with reinforcement in general was responsible for the decreased responding for ethanol [3, 14, 49, 54, 55] This hypothesis would propose that at the high naloxone dose a general overall suppression of reinforcement efficacy results, and thus decreased responding for ethanol (along with a variety of other reinforcers) would occur

In support of this alternative explanation is a large body of work which has found that high doses of naloxone decrease the effectiveness of a wide variety of reinforcers [4, 21, 43, 49] For example, while naloxone decreases the effectiveness of food as a reinforcer, it is doubtful that the effect is a result of specific blockade of metabolic breakdown products of food that normally bind to the brain opiate receptors to produce reinforcement Additional support is provided by research that has shown an interaction of naloxone with non-opiate drugs [8, 16, 18, 26, 27, 34] which would suggest the possibility of such an indirect interaction could occur with ethanol self-administration Thus, a possible confounding factor is that high doses of naloxone interact with receptor systems other than the endogenous opiate system, which alter responding for ethanol

It might be argued that to antagonize the effects of ethanol or its possible metabolic products, larger naloxone doses were required in order to last throughout the operant session These increased doses would be needed to prevent ethanol reinforced responding from recovering in the later part of the session This explanation cannot be accepted for two reasons First, the half life of the 5 mg/kg dose is at least 2 hours [53] Since only one hour elapsed between injection and the end of the session, the receptor antagonism should have been more than adequate for the entire duration of the operant session Second, examination of the cumulative response records following naloxone treatment failed to show any early session effects that were compensated for by increased responding later in the session It would therefore seem that this explanation for the requirement of the higher naloxone dose cannot account for the observed results

Some classes of opiate receptors have low affinity for opiate antagonists and high doses are required for competitive binding at these sites [22, 29, 32] While it is possible that these low affinity naloxone sites are the ones involved in the high dose effects found in this study, the implications of reinforcement maintenance via similar actions of opiates and ethanol at these particular endogenous opiate sites is doubtful The ability of low naloxone doses to alter opiate reinforcement while not affecting oral ethanol self-administration makes the involvement of the same endogenous opiate receptors for both drugs questionable It is quite possible that the opiate receptors which require high antagonist doses are involved in both ethanol and opiate reinforcement, with only the low affinity set activated by ethanol, but given that opiate reinforcement is decreased by low naloxone doses and that many reinforcers are affected by high naloxone doses, a role discussed above, the specific role of the low affinity opiate antagonist receptor for ethanol reinforcement seems questionable

A major problem in proposing that an effect upon reinforcement in general explains the observed decrease in ethanol responding, is the lack of such an effect on responding for sucrose or water with the same naloxone dose This problem is particularly salient for water responding, since only increases were observed (at the 5 mg dose when paired with ethanol and at the 20 mg dose when paired with sucrose) The increased water responding, while statistically significant in each case, represents generally small absolute increases in responding when compared to total session responding At the 5 mg dose in the ethanol-water condition (Experiment 1) water responding went from 20% of the total

responding to 26% of the total responding on drug days. At the 20 mg dose level in the sucrose-water condition (Experiment 2), water responding went from 5% of the total responding to 8% of the total responding on drug days. The most frequent finding in other investigations of naloxone on water intake has been a decrease in drinking (usually in the fluid deprived animal), if any effect is observed at all (see [42] for review) Thus, the significant increases for water responding seen here are most likely due to the low baseline levels of responding and do not represent behaviorally significant intake increases. Since the animals were food deprived, the taste factors of the available fluids may have been important in determining the actual effects of naloxone upon responding There are a variety of studies which have implicated the endogenous opiate system in the regulation of food intake [42] In general, in deprived rats high doses of naloxone are needed to decrease food intake Especially relevant to the present study is the suppression of saccharin and sucrose solution intake in food deprived animals [6, 30, 43, 48, 57] It has been shown that the taste of a given solution (as manipulated by concentration) can alter the amount of decreased intake occurring when high naloxone doses are administered [30] It is possible that, given the taste stimuli associated with 5% ethanol when compared to 1% sucrose, the observed differences between the suppression of ethanol and lack of suppression of sucrose responding could be due to each solution's taste qualities This would suggest that the observed differences between sucrose and ethanol at the 20 mg dose were not results of specific receptor antagonism of ethanol but rather effects of the amount of modulation of endogenous opioids with other reinforcement mechanisms in general The failure to induce maintained responding with 1% sucrose, when using the same induction procedure shown to be successful with 5% ethanol, would indicate that these two substances have distinct qualitative differences as reinforcing stimuli Since sucrose intake has been shown to be suppressed by naloxone under conditions in which higher sucrose concentrations were used [57], it seems possible that the failure to observe a similar decrease in these studies may have been a result of the sucrose concentration used The 1% sucrose concentration was chosen for these studies in order to approximate response patterns similar to those observed in the ethanol condition To the extent that this was successful, it would appear that factors other than response patterns may be important in determining naloxone's effects upon responding Further study with other sucrose concentrations will be needed to clarify this point

Comparison of this study with that reported by Altshuler *et al* [1] indicate only partial agreement as to the effects of narcotic antagonists on ethanol-maintained behavior The major difference in findings between the two studies was the extinction pattern reported by Altshuler *et al* [1] Both studies found that with narcotic antagonist treatment, ethanol responding was still maintained but reduced by approximately 50% The initial increase followed by decreases in ethanol responding reported by Aultschuler *et al* [1] was suggested by these authors to be similar to extinction curves that result from termination of reinforcement [13] They therefore concluded that naltrexone was reducing the efficacy of ethanol reinforcement by blocking its action at the endogenous opiate receptor. It should be pointed out, however, that the pattern of responding reported by Altschuler *et al* is not similar to the response patterns usually found for extinction in general [13], nor for the effect of naloxone or naltrexone pretreatment on morphine maintained responding in either nondependent monkey or rat [15]. There are many experimental differences between the two studies which might account for the discrepancy between the studies (i.e., the use of different species—rats vs. monkeys, routes of ethanol administration—oral vs. IV, narcotic antagonist used—naloxone vs. naltrexone, dosage regimen employed—acute vs chronic, etc.). There is however, a possibility of an alternative explanation of the Altschuler *et al* data Since chronic dosing with naltrexone leads to sensitization of the response to the drug [34, 46, 52, 58], the Altschuler *et al* results of decreased responding observed only after several days of chronic treatment may have resulted from an increased sensitivity to and accumulation of the antagonist. This accumulation and sensitization could result in an effect similar to a single acute larger dose, a dose which could produce alteration of reinforcement in general, in a manner similar to that proposed above Since no controls for effects of the dosage procedure upon other reinforcers were included in the Altshuler *et al* study [1], nor were daily food and water intakes presented, the possibility of a nonspecific alteration of reinforcement systems in general seems a tenable alternative interpretation for their observed decrease in ethanol intake.

It has been proposed that the dopaminergic system may play a major role in reinforcement (ethanol reinforcement included) [54,55]. There are implications for the modulation of this dopaminergic reinforcement system by endogenous opiates, and in particular, the opiate receptors that may only be affected by high doses of opiate antagonists [55] What role this dopaminergic-endorphinergic reinforcement system may play in both ethanol- and opiate-maintained behavior remains to be more thoroughly examined. This interactive system would not require the production of any opiate-like receptor substance to produce ethanol reinforcement, but would make ethanol-maintained behavior susceptible to high doses of narcotic antagonists as is behavior maintained by other classes of reinforcers (e g., food, water, sex, etc).

In summary, since only relatively large doses of naloxone affected ethanol responding, a result in marked contrast to the effect of narcotic antagonists on morpine self-administration [11], it seems unlikely that direct receptor activity by ethanol or its metabolites at the endogenous opiate system is involved in the maintenance of oral ethanol self-administration in the rat. Many studies have shown suppressant effects of naloxone on responding for a variety of reinforcers [4, 21, 43, 49] and thus, the endogenous opiate system has been implicated in reinforcement systems in general [3, 14, 49, 54, 55]. Given that only high doses of naloxone had any effect upon ethanol responding, rather than proposing that ethanol or its metabolic products are acting at the opiate receptor to maintain oral ethanol self-administration, it would seem more reasonable to assume that at high or prolonged opiate antagonist doses, the reinforcing capabilities of ethanol along with a wide variety of other reinforcers are decreased This implies that the reinforcing systems that are responsible for the maintenance of oral ethanol intake, while involved with the endogenous opiate system indirectly, are not specifically mimicking opiates in their action, and are reinforcing due to other mechanisms.

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