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Central vs. Peripheral Mediation of Opioid Effects on Alcohol Consumption in Free-Feeding Rats

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LINSEMAN, M. A. *Central vs. peripheral mediation of opioid effects on alcohol consumption in free-feeding rats*. PHARMACOL BIOCHEM BEHAV 33(2) 407–413, 1989.—Although there is considerable evidence that pretreatment with low doses of opioid agonists can enhance, and opioid antagonists can reduce alcohol consumption in rats, little is known about the locus or mechanism of these effects. As a first approximation as to where the effect may occur, we compared the effects of an opioid agonist morphine (1, 3 and 10 mg/kg) and antagonist naltrexone (1, 3 and 10 mg/kg) that are known to act within the brain as well as the periphery, to those of an agonist-like drug loperamide (0.3, 1 and 3 mg/kg) and an antagonist methylnaltrexone (3, 10 and 30 mg/kg) that are known to act peripherally only. Free-feeding rats were initially trained to drink alcohol using a limited access paradigm, and when animals were drinking asymptotic amounts of 12% (w/v) alcohol, increasing doses of one of the four drugs or saline were administered IP to separate groups of rats 30 min prior to the hour-long daily drinking session. The results confirmed that the effects of the opioids on alcohol consumption are indeed mediated within the central nervous system in that morphine enhanced alcohol consumption but loperamide did not, naltrexone reduced alcohol consumption but methylnaltrexone did not, and naltrexone was able to block the morphine effect but methylnaltrexone failed to do so. An unexpected finding was that methylnaltrexone alone also increased alcohol consumption. Possible means by which this could occur, also supporting the idea of a central locus for the effect, as well as possible mechanisms by which opioids could influence alcohol consumption generally, are discussed.

Alcohol Ethanol Consumption Self-administration Drinking Opioids Morphine Naltrexone Loperamide Methylnaltrexone

THERE is now considerable evidence that low doses of opiates affect alcohol consumption. Administration of opiate agonists generally increases consumption, while administration of opiate antagonists decreases it (2, 9, 13, 14, 23, 27), although the exact mechanisms and loci of the effects are still unknown. In regard to localization, an important initial determination to be made is whether the action of the drug is within the central nervous system or in the periphery only. It is possible to do this, in the case of opiates, by comparing the effects of drugs which distribute throughout the body, including the brain, to those of drugs which act only peripherally (i.e., do not cross the blood-brain barrier at the doses used). In this regard, a previous study (12) showed that the peripherally acting opiate antagonist, methylnaltrexone (one dose on one occasion), did not mimic the effect of naltrexone on alcohol consumption, thus suggesting a central site of action. However, we believed this issue merited a more thorough examination.

First, it is important that there be an unequivocal answer to this question before attempting to study the effects of central manipulations of the opiate systems on alcohol consumption, which may be necessary for a full understanding of the effect. Secondly, there is reason to believe that peripheral effects of opiates could well have an effect on alcohol consumption, since it is well known, for example, that opiate agonists have effects on the gastrointestinal tract, delaying stomach emptying and decreasing intestinal motility (15,28). Both of these effects could modify the pharmacokinetics of alcohol, specifically its rate of absorption. Rate of absorption of alcohol is an important determinant of the effects of alcohol (11,21) and several studies in animals have shown that slower absorption of alcohol may favour increased consumption by rats (4, 16, 18). Conversely, opiate antagonists have opposite effects on the gut and their administration has been shown specifically to increase the rate of entry of alcohol into the blood stream following intragastric administration (5), which could by the same reasoning decrease the amount of alcohol consumed.

Thirdly, although it is possible, it is not necessarily the case that effects of opiate agonists and antagonists on alcohol consumption are mediated by the same mechanism. For example, in the case of feeding, although methylnaltrexone, the peripherally acting antagonist, does not reduce amount eaten as does naltrexone, the peripherally acting agonist-like compound loperamide (24) apparently increases feeding as had been found with the

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centrally acting opiate agonists, e.g., morphine (30). In the case of alcohol consumption, although methylnaltrexone apparently did not reduce alcohol consumption (12), the effects of a peripherally acting agonist on alcohol consumption have not been studied.

Finally, many of the previous studies of the effects of opiates have used drinking paradigms in which the alcohol was sweetened and/or the animals were fluid-deprived (and therefore possibly also somewhat food-deprived as a result). Opiates are known to affect consumption of saccharin solutions (8) and to affect deprivation-induced feeding (20,22) and drinking (7); therefore, under these conditions the effects on alcohol per se are not unequivocal.

We have recently described a limited access paradigm in which animals are given relatively high concentrations of unadulterated alcohol to drink during daily drinking sessions but are otherwise allowed ad lib access to food and water. This drinking paradigm has been shown to result in the attainment of chemically measureable (18) and behaviorally significant (10,31) blood alcohol levels. In this paper, we report the effect of prior injections of both centrally acting and peripherally acting agonists and antagonists, over periods of several days and at several doses, on alcohol consumption in this limited access paradigm. In addition, we tested the ability of both types of opioid antagonists to block the agonist effect.

METHOD

Subjects

Subjects of the experiment were 60 male Wistar rats weighing about 300 g at the start of the experiment. They were singly housed in hanging wire cages where food (Purina rat chow) and water were available at all times. They were adapted over a period of two weeks and maintained thereafter on a reverse 12/12 hour dark/light cycle, the dark period beginning each day at 7 a.m.

Animals were randomly divided into two squads of 30 animals each. The drinking session for the first squad began at approximately 10:30 a.m., for the second, at 2:30 p.m. each day. Since drinking sessions were scheduled during the dark period, a single red light bulb was used to illuminate the room throughout the drinking session for the convenience of the experimenter. In addition, a single shaded white light bulb was illuminated in a remote corner of the room during the periods that syringes were prepared and data recorded.

Procedure

Acquisition. All animals were trained to drink alcohol using a limited access procedure similar to that described previously (18,19). Animals were weighed daily before being transferred to separate individual "drinking" cages, also within the colony room, where two modified Richter tubes, one containing increasing concentrations of alcohol and the other, tap water, were presented approximately 20 minutes later. The concentration of alcohol was 3% w/v (in tap water) over the first 14 days, was increased to 6% for Days 15 to 28, and to 12% from Day 29 onward. One hour after the presentation of the solutions, amounts of alcohol and water drunk were recorded to the nearest 0.1 ml, corrected for spillage, and the animals were returned to their home cages. Fresh alcohol and water solutions were provided daily, and the positions of the alcohol and water tubes were alternated daily to control for possible position preferences.

Phase 1: Drug Treatment Period

Following the acquisition period, animals were divided into five groups matched on the basis of their alcohol consumption (g/kg) over Days 39 to 44. The five groups were randomly designated to serve as a saline control group, a morphine group, a loperamide group, a naltrexone group and a methylnaltrexone group. The daily procedure continued as before except that after weighing and before being placed in the drinking cages, all animals were injected with one of the five drug solutions, according to their group assignment. All injections were IP, in a volume of 1 ml/kg. All drugs were dissolved in saline with the exception of loperamide which required the addition of Tween 80 (2 drops/10 ml) to form a solution or very fine suspension (depending on the concentration) in the saline. The period of time between injections and availability of alcohol was about 30 minutes.

Injections continued daily across 18 days. Three doses of each drug, in semilogarithmic steps, in ascending order, were administered, each for a period of 6 days. Doses of morphine were 1, 3 and 10 mg/kg; of loperamide, 0.3, 1 and 3 mg/kg; of naltrexone, 1, 3 and 10 mg/kg; and of methylnaltrexone, 3, 10 and 30 mg/kg. Following the series of drug injections, drinking sessions continued as before, without any prior injection for the next 10 days in order to evaluate possible withdrawal effects and to establish a new baseline.

Phase 2: Test for Blockade of the Agonist Effect by the Two Antagonists

When drinking had returned to its predrug levels and was once again stable, all animals were divided anew into 5 groups matched on the basis of their alcohol consumption over Days 67 to 72. Four groups were randomly designated to serve as a saline (pretreatment)-saline (treatment) group, a saline-morphine group, a naltrexone-morphine group and a methylnaltrexone-morphine group. The fifth group continued through this phase as a saline-saline group as well.

During this phase of the experiment, animals were removed from their home cages, weighed, given their pretreatment injections and returned to their home cages. After a period of approximately 30 minutes, they were again removed from their home cages, given their treatment injections and placed into their drinking cages. Alcohol and water were then presented in their drinking cages after another period of approximately 30 minutes. Amounts of alcohol and water drunk after one hour were recorded as before. All injections were IP, in saline, in a volume of 1 ml/kg. The pretreatment dose of naltrexone was 3 mg/kg; of methylnaltrexone, 10 mg/kg. The treatment dose of morphine was always 3 mg/kg. This phase continued for 6 days (Days 73–78). The following day (Day 79), injections continued for the saline-saline group and for the saline-morphine group, while the remaining rats were returned to the regular drinking schedule without injections. On Day 79, animals of the saline-saline and saline-morphine groups were removed from their drinking cages 30 min after the beginning of alcohol availability. At that time a 50 microlitre sample of blood was withdrawn from their tails for assessment of blood alcohol level (BAL) according to a procedure previously described (19). Normal drinking sessions, without any injections, then continued for all animals for an additional 7 days (Days 80–86).

Phase 3: Tween 80 Control

In Phase 1, Tween 80 had to be added, unexpectedly, to the saline vehicle to allow the loperamide to go adequately into solution, but no control for this had been included in the original design of the experiment. Accordingly, we examined the effects of this dilute solution of Tween 80 alone on alcohol consumption.

TABLE 1

EXPERIMENTAL SCHEDULE

	Alcohol Concentration	Days
1. Acquisition	3%	1–14
	6%	15–28
	12%	29–44
2. Drug Treatment Dose 1	12%	45–50
(Phase 1) Dose 2	12%	51–56
Dose 3	12%	57–62
3. Return to Baseline	12%	63–72
4. Blockade by Antagonists (Phase 2)	12%	73–78
5. Return to Baseline	12%	80–86
6. Effect of Tween (Phase 3)	12%	87–92
7. Return to Baseline	12%	93

Since not all animals were required for this purpose, only the animals of Squad 2, whose drinking session was scheduled in the afternoon, were used. They were divided into two new groups (n = 15) matched on the basis of their alcohol consumption on Days 81 through 86. The two groups were randomly designated a saline control group and a Tween experimental group. During this phase (Days 87 to 92) animals were injected IP with either saline or Tween 80 (2 drops/10 ml saline) IP, in a volume of 1 ml/kg prior to being placed in their drinking cages each day. Alcohol and water became available approximately 30 min following the injection. After six days, animals were subjected to the drinking procedure for one additional day (Day 93) without any prior treatment, to determine whether there would be any withdrawal effects as had been observed in the group for which Tween was used as a solvent earlier.

A summary of these procedures is shown in Table 1.

Drugs

Drugs used were morphine sulphate (BDH), naltrexone hydrochloride (Sigma), methylnaltrexone (naltrexone methobromide, MRZ 2663 BR, Boehringer Ingleheim), and loperamide hydrochloride (Sigma).

Statistical Analysis

All data were analyzed by one-way analyses of variance for matched groups, with comparisons being made in regard to overall averages, and possible linear and quadratic trends, between the groups of interest. A statistically significant difference was considered to be one for which $p<0.05$ on a two-tailed test.

RESULTS

Phase 1

The effects of the various drug treatments on doses of alcohol consumed are shown in Fig. 1; on the relative volumes of alcohol and water consumed, in Fig. 2.

In regard to agonist treatments, there was an overall increase in alcohol consumption by the morphine group as compared to the saline group throughout the period of treatment, $F(1,10)=31.91$, $p=0.000$. In addition, the difference in alcohol consumption between the morphine and saline groups was different at each individual dose level [1 mg/kg: $F(1,11)=20.65$, $p=0.001$; 3 mg/kg: $F(1,11)=31.03$, $p=0.000$; 10 mg/kg: $F(1,10)=10.97$, $p=0.008$]. There was, as well, an increasing effect over days of treatment at the lowest dose (1 mg/kg) as indicated by a significant linear trend between the morphine and saline groups, $F(1,11)=5.98$, $p=0.033$. Morphine also had a significant effect on water consumption. That is, water consumption was significantly decreased at the two lower doses of morphine [1 mg/kg: $F(1,11)=5.58$, $p=0.038$; 3 mg/kg: $F(1,11)=7.89$, $p=0.017$] although this was no longer true of the 10 mg/kg dose, $F(1,10)=0.79$, $p=0.395$.

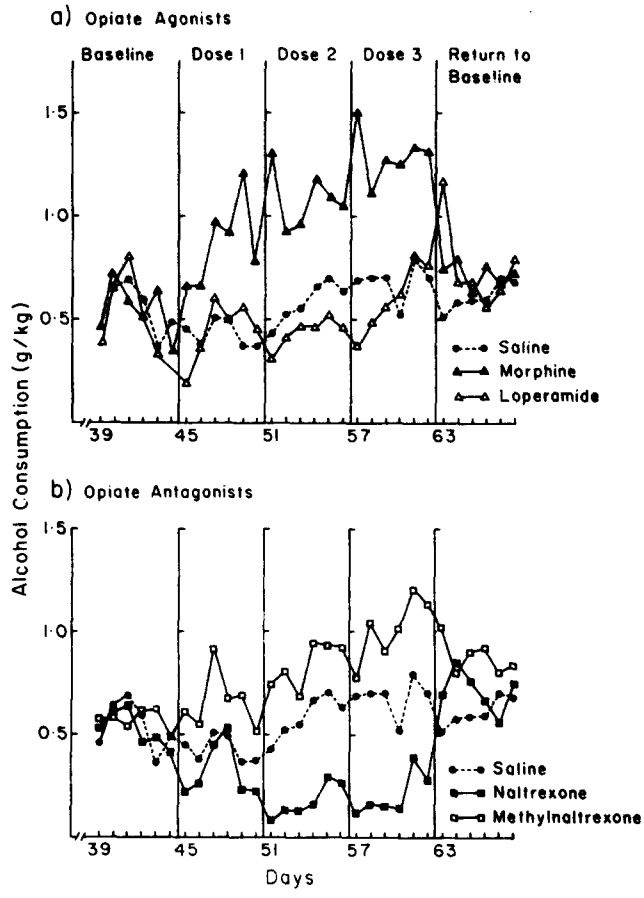

FIG. 1. Mean alcohol consumption (g/kg) over days by groups of animals receiving treatment with (a) the opiate agonist morphine or the opiate agonist-like loperamide and (b) the opiate antagonists in Phase 1 of the experiment.

By contrast, there were no significant differences in mean alcohol consumption between the loperamide and saline groups either across the period of treatment, $F(1,10)=2.11$, $p=0.177$, or across any individual dose used. Nevertheless, loperamide increased water consumption significantly. That is, there was an overall significant difference between the loperamide and saline groups across the period of treatment, $F(1,10)=21.01$, $p=0.001$, and across each of the individual doses [0.3 mg/kg: $F(1,11)=8.61$, $p=0.014$; 1 mg/kg: $F(1,10)=17.93$, $p=0.002$; 3 mg/kg: $F(1,11)=17.40$, $p=0.002$].

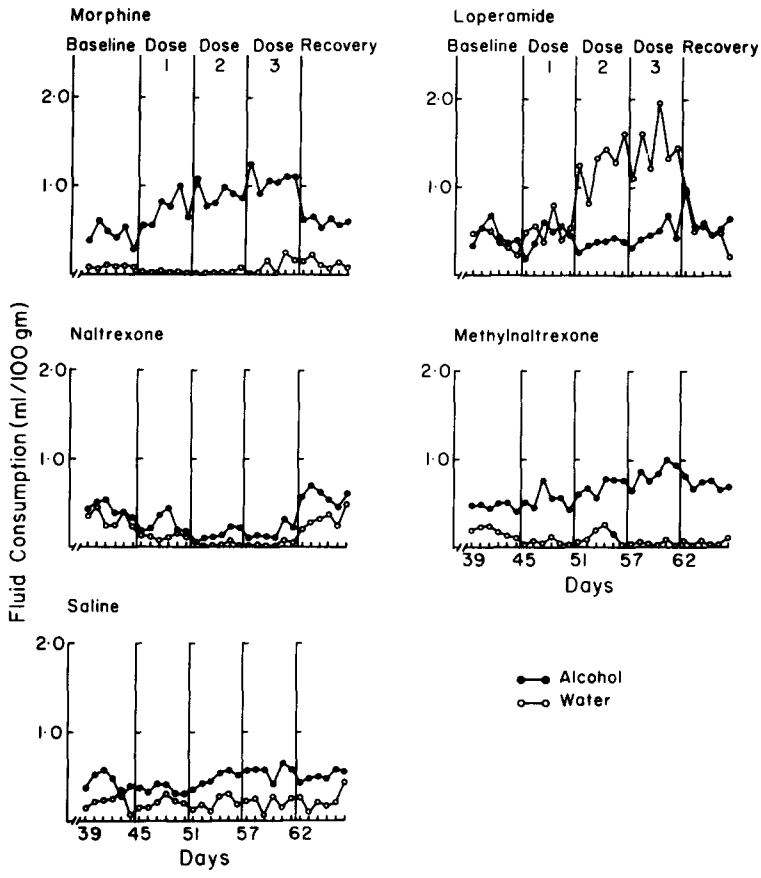

FIG. 2. Mean volumes of alcohol and water consumed over days by the five groups of animals, i.e., morphine, loperamide, naltrexone, methylnaltrexone and saline in Phase 1.

In regard to the antagonist treatments, naltrexone resulted in a significant decrease in alcohol consumption compared to the saline group across the 18-day treatment period, $F(1,10) = 37.77$, $p = 0.000$. In terms of individual doses, there was no significant difference between the two groups at the 1 mg/kg dose, $F(1,11) = 1.18$, $p = 0.301$, but the differences at the 3 and 10 mg/kg doses were highly significant [3 mg/kg: $F(1,10) = 28.61$, $p = 0.000$; 10 mg/kg: $F(1,11) = 40.86$, $p = 0.000$]. Naltrexone also, however, decreased water consumption relative to the saline group. This effect was significant across the 18-day treatment period, $F(1,10) = 5.65$, $p = 0.039$, and at the two highest doses [3 mg/kg: $F(1,10) = 6.37$, $p = 0.030$; 10 mg/kg: $F(1,11) = 7.39$, $p = 0.020$].

Methylnaltrexone, by contrast, did not produce a decrease in alcohol consumption as did naltrexone, but surprisingly, resulted in increased alcohol consumption relative to the saline group. This was reflected by a significant overall difference between the methylnaltrexone and saline groups across the period of treatment, $F(1,11) = 32.74$, $p = 0.000$, and across each of the individual doses [3 mg/kg: $F(1,11) = 12.97$, $p = 0.004$; 10 mg/kg: $F(1,11) = 7.63$, $p = 0.018$; 30 mg/kg: $F(1,11) = 21.38$, $p = 0.001$]. Although methylnaltrexone, like morphine and naltrexone, decreased water consumption, this effect was significant only at the highest dose, $F(1,11) = 6.76$, $p = 0.025$.

Phase 2

The results of the attempts to block the morphine effect with the two antagonists are illustrated in Fig. 3.

As in Phase 1, morphine treatment significantly increased alcohol consumption as reflected by a significant difference between the saline/saline and saline/morphine groups, $F(1,11) =$

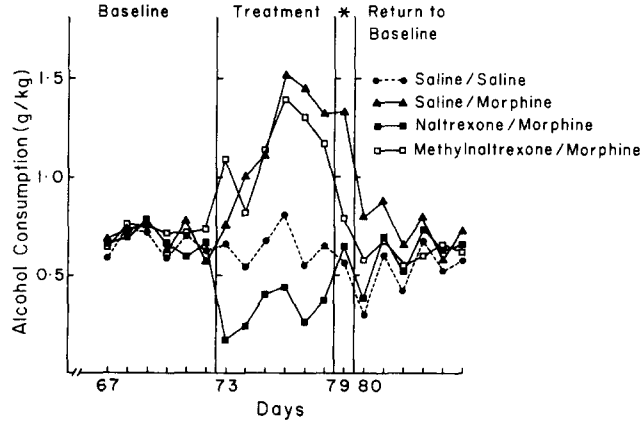

FIG. 3. Mean doses of alcohol consumed by the four groups during Phase 2. On Day 79 (*) the saline/morphine and saline/saline groups continued to receive pretreatment/treatment injections, while the other two groups did not.

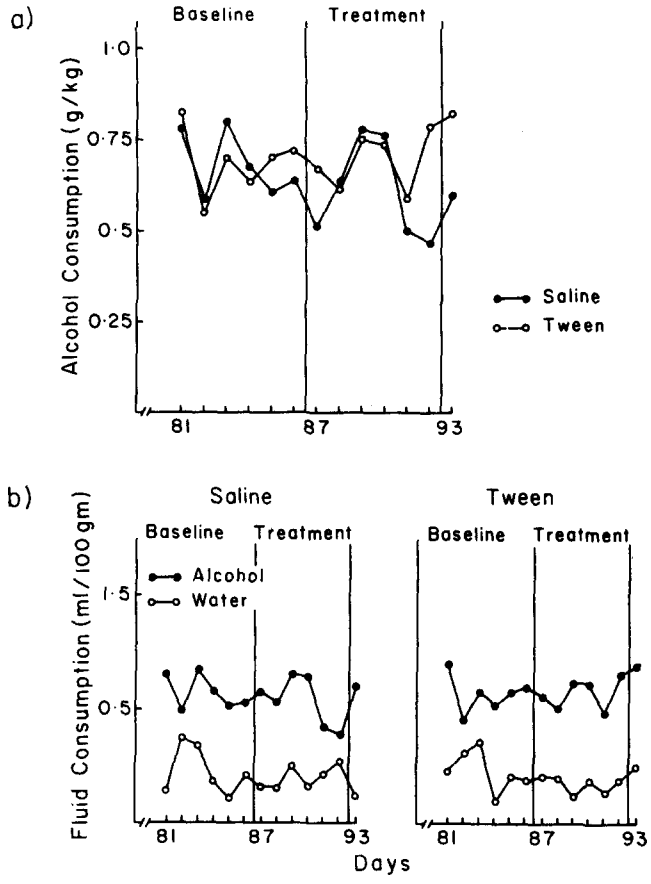

FIG. 4. (a) Mean doses of alcohol consumed and (b) mean volumes of alcohol and water consumed by animals pretreated with either Tween or saline prior to availability of alcohol in Phase 3.

21.24, $p=0.001$. In addition, as in Phase 1, there was an increasing effect of the morphine treatment over days as evidenced by a significant linear trend between the two groups, $F(1,11)=24.63$, $p=0.000$. Administration of naltrexone prior to morphine blocked the morphine effect as indicated by a significant difference between the saline/morphine and naltrexone/morphine groups, $F(1,11)=55.74$, $p=0.000$. However, pretreatment with methylnaltrexone failed to alter the morphine effect, i.e., there was no difference between the saline/morphine and methylnaltrexone/morphine groups, $F(1,11)=0.08$, $p=0.68$. There was also a significant difference between the naltrexone/morphine and saline/saline groups, $F(1,11)=13.18$, $p=0.004$.

Mean BAL of the saline/morphine group on Day 79, 30 minutes following availability of alcohol, was 52.5 ± 5.7 (s.e.m.) mg%, of the saline/saline group, 33.8 ± 7.7 mg%, $F(1,11)=5.46$, $p=0.038$.

Phase 3

The effects of the Tween vehicle injections compared to saline on alcohol and water consumption are illustrated in Fig. 4. There was no difference between the Tween and saline groups either during the period of treatment on consumption of either alcohol, $F(1,14)=0.40$, $p=0.54$, or water, $F(1,14)=0.21$, $p=0.65$, nor were there any differences on the following day.

DISCUSSION

The results of this experiment clearly indicate that the effects of opioid agonists and antagonists on alcohol consumption are mediated within the central nervous system. That is, morphine enhanced alcohol consumption; loperamide, the peripherally acting agonist-like compound, did not. Conversely, naltrexone reduced alcohol consumption; methylnaltrexone, the quaternary derivative that does not cross into the brain, did not. In addition, in Phase 2, although naltrexone antagonized the effect of morphine, methylnaltrexone did not.

An unanticipated result of this experiment was the seemingly paradoxical increase in alcohol consumption by the methylnaltrexone-treated animals. However, this result too may support the main conclusion. That is, it is possible that a peripheral opioid receptor blockade, in the presence of an equivalent amount of circulating endogenous opioids, may effectively result in an increased concentration of opioids within the central nervous system (the effective site of action). Alternatively, as is the case for many neurohormones, blockade, especially daily or chronic, of opiate action in the periphery might, as a result of negative feedback, lead to an upregulation within the endogenous opioid system. This could result in an enhancement of alcohol consumption just as does administration of exogenous opioids. Of related interest, systemically-administered methylnaltrexone has been reported to produce a place preference (3) and hot plate analgesia (17) possibly by a similar mechanism. Together, the enhancement of alcohol consumption by methylnaltrexone, plus the low dose of morphine required to increase alcohol consumption, suggest the effect can be produced within the physiological range of the endogenous opioid system. These low dose effects were even more impressive when compared to the effects in this laboratory of prior administration of various dopaminergic agonists and antagonists on alcohol consumption using the same paradigm, where increases in alcohol consumption were never observed, and decreases resulted only after administration of doses that were sufficiently high to cause nonspecific motor effects (in preparation).

The administration of morphine produced an increase in alcohol consumption which appeared to strengthen over days in both Phases 1 and 2. There are at least two interpretations of this effect although it is not possible to choose between them with the present data. One is that it may be a chronic effect of morphine administration rather than an acute effect that is related to increased alcohol consumption. For example, there is sensitization in regard to the locomotor stimulating effects of chronic administration of low doses of opiates (1) and psychomotor stimulant effects have been hypothesized to be the basis of reinforcement by psychoactive drugs (29). Alternatively, the increase in alcohol consumption over days of treatment may reflect a learning effect, which, in the case of oral alcohol consumption, is quite conceivable. That is, in the case of alcohol in a limited access paradigm, consumption of the alcohol usually occurs in a single bout at the beginning of the session and seemingly concludes before adequate time has elapsed for the pharmacological effects of the alcohol to be experienced. The event to be affected by the treatment therefore would seem to be the bout rather than individual licks, and modification of the behavior would be more likely reflected over sessions than within sessions. By contrast, in the case of intravenous administration of stimulants or opiates, for example, the pharmacological effect of the drug is more immediately experienced and within-session compensation to the effects of treatment would occur, such as in the "extinction burst" or momentary increase in responding to an apparent decrease in reinforcing efficacy following certain types of receptor blockade. According

to this reasoning, a maximal change in alcohol consumption on the first day of treatment might be more likely to reflect a performance change than a change in the reinforcing effects of alcohol itself. In this regard, it would be interesting to compare the effects of pharmacological blockers on both oral etonitazene and alcohol consumption in a limited access paradigm to determine whether the pattern of effect is due to the specific drug or to the route of administration.

Another interesting feature of the data is the large increase in water consumption caused by pretreatment with loperamide. This confirms, first of all, that the doses of loperamide used were sufficient to produce physiological effects, but it also suggests that the increase in fluid consumption in response to pretreatment with opiate agonists may be in response to their peripherally mediated constipating effects. Nevertheless, morphine-pretreated animals showed a definite, in fact increased, preference for alcohol, whereas the loperamide-pretreated animals did not.

The functional mechanism(s) by which the opioid agonists and antagonists alter alcohol consumption is still not known. It is possible that opioids could affect the appetitive characteristics of alcohol. This could occur directly if positive reinforcement by alcohol was mediated via the opiate receptor (6). Alternatively, the opioids could act indirectly to facilitate reinforcement by alcohol by enhancing activity within the pathway that normally mediates reinforcement by alcohol. Conversely, the opioids could interfere with mechanisms that would normally stop further consumption of alcohol. As alluded to in the introduction, opioids could alter alcohol self-administration by affecting the rate of absorption of alcohol. Although the results of this experiment make it clear that if this were the case, these effects are not mediated peripherally, it is still possible that they could result from the actions of opioids within the brain (25). Finally, opioids could affect the level of intoxication produced by a given dose of alcohol [e.g., (26)], pharmacokinetically or pharmacodynamically, so that the signal to stop drinking is advanced or delayed, resulting in modified consumption. Further research should explore these various possibilities.

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