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Effects of Opioids on the Absorption of Alcohol

M. A. LINSEMAN[1] AND A. D. LÊ

Addiction Research Foundation of Ontario, Toronto, Ontario M5S 2S1, Canada
Department of Pharmacology, University of Toronto, Toronto, Ontario, M5S-1A8 Canada

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LINSEMAN, M. A. AND A. D. LÊ. *Effects of opioids on the absorption of alcohol.* PHARMACOL BIOCHEM BEHAV **58**(1) 79–84, 1997.—Administration of opiate agonists and antagonists has been shown to increase and decrease alcohol consumption, respectively. Because opioids can affect gastric emptying and decrease intestinal motility, the present experiments were done to determine whether changes in alcohol consumption following opioid administration might be due to opioid-induced changes in the pharmacokinetics of alcohol. In experiment 1, morphine in doses ranging from 1.5 to 4.5 mg/kg dose dependently decreased the absorption of alcohol induced by oral intubation (1 g/kg) and reduced peak blood alcohol levels (BALs). Naltrexone in doses ranging from 1.5 to 4.5 mg/kg produced a small, but significant, reduction in the absorption of alcohol, but the effects were not dose related. Similar effects of morphine and naltrexone on alcohol absorption were observed in rats infused with alcohol (1 g/kg) through an implanted intragastric cannula. The effects of morphine on alcohol absorption were observed whether alcohol levels were determined from tail vein or arterial blood samples or from brain samples. The effects of morphine on alcohol absorption were not blocked by pretreatment with methyl-naltrexone. However, the peripherally acting opioid agonist loperamide reduced BALs in a manner similar to morphine. These studies indicate that although opiate agonists and antagonists modify alcohol absorption to different extents, their effects on BALs are not a sufficient condition to induce changes in alcohol consumption. © 1997 Elsevier Science Inc.

Alcohol Morphine Naltrexone Loperamide Pharmacokinetics Blood alcohol levels Absorption Consumption

THE INVOLVEMENT of endogeneous opioid systems in alcohol intake has been a subject of interest over the last several years. Systemic administration of low doses of opiate agonists has been shown to increase subsequent alcohol consumption by rats, and administration of opiate antagonists has been shown to decrease it (4,7–9,18,19,25,26). These effects appear to be mediated within the brain, because opiate agonists and antagonists that do not cross the blood–brain barrier do not affect alcohol consumption (18) and because intracerebroventricular administration of a very low dose of morphine also causes increased alcohol consumption (19).

Opioids have been shown to have profound effects on the gastrointestinal (GI) tract, slowing gastric emptying and reducing intestinal motility (12,13,23). These effects can be produced directly by stimulation of opiate receptors within the stomach and intestine and indirectly by acting on receptors within the central nervous system (12,13). Opioids could thereby modify the absorption of alcohol and the blood alcohol levels (BALs) achieved after oral administration or consumption. There is considerable evidence that consumption of alcohol in single bouts at least is regulated by its pharmacological consequences (18,31) and that reduced rates of absorption are associated with increased consumption (1,17). Opioids thus could affect alcohol consumption indirectly by altering its rate of absorption into the blood. A number of previous experiments have studied the effects of opioids on BALs, but often the alcohol was not administered intragastrically, which is the route of interest when one is attempting to make inferences about alcohol consumption (6), or the opioids were administered at various times after the administration of alcohol, when they would no longer affect the initial absorption of alcohol (2).

In this paper, we describe a series of experiments in which several opiate agonists and antagonists were administered prior to oral administration of a low dose of alcohol (comparable to that voluntarily consumed in a single bout by rats) and their effects on alcohol kinetics were examined. In the first experiment, the effects of several doses of opiate agonists and antagonists on BALs produced by oral intubation of 1 g/kg of alcohol were examined. In the second series of experiments, alcohol was administered via chronically implanted nasogastric tubes to minimize the stress associated with oral in-

[1] Present address: Medical Research Council, Ottawa, Ontario, Kiaowg, Canada. This work was carried out while M. A. L. was at the Addiction Res. Foundation.

Requests for reprints should be addressed to A. D. Lê, Addiction Research Foundation, 33 Russell Street, Toronto, Ontario M5S 2S1, Canada.

tubation, which would otherwise itself significantly affect the absorption of alcohol. This design was chosen to mimic as closely as possible the experimental conditions under which administration of opioids has been shown to modify alcohol consumption, to be able to evaluate the possibility that changes in consumption may be related to altered levels of alcohol in the body. Morphine and naltrexone in doses that have previously been shown to increase and decrease alcohol consumption, respectively (18), were employed in these studies.

MATERIALS AND METHODS

Animals

Male Wistar rats weighing 250–300 g were obtained from Charles River Laboratories (Montreal, Quebec, Canada). They were housed singly and fed a standard rat chow diet with food and water available ad lib. To minimize the effects of food consumption on alcohol absorption, food was removed from the hoppers 2 h prior to pretreatment with opiate agonists or antagonists and was restored at the end of testing. The temperature of the colony room was maintained at 21 ± 1°C, and lights were on from 0700 to 1900 h daily throughout the experiments. All testing was carried out between 1000 and 1500 h.

Implantation of Nasogastric Tubes

Nasogastric tubes were implanted in all animals under pentobarbital anesthesia [50 mg/kg intraperitoneally (IP)] in a manner similar to that described by Kissileff (11) except that PE 10 tubing was extended by PE 50 tubing, which was passed subcutaneously and externalized at the back of the neck. The PE 50 tubing was ultimately fed through an inverted drilled out plastic bolt, and this assembly was anchored subcutaneously in a collar of Marlex mesh. Although there was some attrition, in general this procedure allowed the cannulae to remain functional for a period of several months. Following surgery, animals were allowed to to recover until they were eating and drinking normally and had returned to their preoperative weight. During this time, as well, they were infused several times per week with 5 ml of water to prevent the tips of the cannulae from becoming obstructed and to accustom the animals to the handling that was associated with intragastric infusion.

Drugs

All drug solutions were freshly prepared on the day of experiments. Alcohol was dissolved in tap water as a 12% (w/v) solution. All other drugs (morphine, naltrexone, methyl-naltrexone, and loperamine) were dissolved in saline in concentrations such that the volume of injection was 1 ml/kg of body weight.

Blood and Brain Ethanol Determinations

Blood samples (50 μl each) were taken from the tip of the tail of each rat at various time intervals after alcohol administration for determination of blood alcohol levels. During the collection of blood samples, rats were restrained in a cone made from a hard paper binder. Collection of each blood sample from the rat took an average of 30 s. In experiment 1, blood samples were collected at 15, 30, 60, 90, 120, and 180 min after administration of alcohol. In the second experiment, blood samples were collected 5, 10, 15, 20, 25, 30, 45, 60, 90, 120, and 180 min after infusion of alcohol. The concentration of alcohol in the blood was determined by gas chromatography with *n*-butanol as internal standard (15,17).

To determine brain alcohol concentration, animals were killed by cervical dislocation 7.5 min after oral administration of alcohol. Brains were rapidly removed and rinsed with 0.5 ml of 0°C saline. Brains were then blotted dry, weighed, and homogenized in sufficient solution of perchloric acid (25 mM)/thiourea (0.6 M) to bring the total volume of the homogenate to 10 ml. Samples were frozen at −80°C for later analysis of brain alcohol content. At that time, a 50-μl sample of the brain homogenate was analyzed by gas chromatography using a 2-foot glass column, i.d. 4 mm, packed with Halciomid M18 on Poropak 80/100 mesh. A 50 μl sample of blood was also drawn from the left ventricle simultaneously with the removal of the brain, and this was analyzed in the same way as the other blood samples.

Experiment 1

The first experiment was designed to examine the effects of various doses of morphine and naltrexone on the absorption and elimination of 1 g/kg of orally administered alcohol. Thirty-two rats were used for the study. They were randomly divided into four groups with $n = 8$ per group and were designated to receive pretreatment with 0.0, 1.5, 3, or 4.5 mg/kg of morphine 30 min prior to oral intubation with 1 g/kg of alcohol. Blood samples were then collected at various intervals from the tails of the animals as described above.

One week later, the same animals were randomly reassigned to four groups, $n = 8$ each, and were designated to receive pretreatment with 0.0, 1.5, 3.0, or 4.5 mg/kg of naltrexone 30 min prior to alcohol intubation.

Experiment 2

The second experiment was designed to extend the observations on inhibition of alcohol absorption made in experiment 1. To minimize the stress associated with oral intubation through an intragastric needle, rats ($n = 24$) were implanted with intragastric cannulae through which alcohol solution was delivered as described above. The experiment consisted of four different phases.

In phase 1, the effects of IP pretreatment with morphine and naltrexone on alcohol kinetics were investigated. The IP route of administration was employed to determine the possible differences in the effects of these agents on alcohol kinetics and to provide appropriate comparison to the loperamide study (phase 2), which also used IP administration. To examine the effects of morphine on alcohol kinetics, rats were divided into two groups ($n = 12$ each) and were designated to receive pretreatment with saline or morphine (3 mg/kg IP) 30 min before the infusion of 1 g/kg of ethanol. Blood samples were collected from the tail vein of the rat 5, 10, 15, 20, 25, 30, 45, 60, 90, 120, and 180 min following alcohol administration for determination of alcohol levels. The effects of IP administration of naltrexone (3 mg/kg) on alcohol kinetics were examined 1 week later in the same animals. Rats were randomly reassigned to two groups and received pretreatment with saline or naltrexone 30 min prior to alcohol administration.

In the second phase, the effect of loperamide on alcohol kinetics was examined. Loperamide has effects on the GI tract similar to those of morphine (19) but does not affect alcohol consumption (15). The design for this phase of the experiment was similar to that of phase 1. Loperamide hydrochloride (1 mg/kg) was administered 30 min prior to infusion of 1 g/kg of alcohol. Control animals received an equivalent

volume (1 ml/kg) of the Tween vehicle (2 drops Tween in 10 ml saline).

In the third phase of the experiment, the ability of methyl-naltrexone (10 mg/kg), an opiate antagonist that does not cross the blood–brain barrier, to antagonize morphine-induced inhibition of alcohol absorption was investigated. Rats were randomly divided into two groups (n = 12 each) and were treated with saline or morphine (3 mg/kg IP) 30 min before alcohol administration. Each of the morphine and saline treatment groups was also divided into two equal subgroups, one of which received a pretreatment with methyl-naltrexone 30 min prior to the treatment with morphine or saline; the second half of each group received an IP injection of saline. One week later, the same two treatment groups were retained, i.e., morphine and saline, but pretreatments were reversed such that rats that had received methyl-naltrexone the previous week received an injection of saline 1 h before the alcohol, and those that had received a saline pretreatment the previous week received an injection of methyl-naltrexone.

In the first and second phases of experiment 2, all blood samples were drawn from the tail vein, which is believed to represent mixed arterial–venous blood. Although alcohol equilibrates rapidly in the body, arterial blood generally has higher alcohol levels than venous blood immediately following alcohol administration (20,27,29), and arterial and brain levels are more likely to determine the behavioral effects of alcohol (5,20). Consequently, in the third phase of experiment 2, arterial blood (from the left ventricle) and brain alcohol levels were determined 7.5 min after alcohol administration (1g/kg) in rats pretreated with morphine (3 mg/kg IP) or saline.

Data Analysis

Two-way analysis of variance (ANOVA) was used to evaluate the effects of opioid agonists and antagonists on BALs. Newman–Keuls tests were used for post hoc testing where appropriate. Student's unpaired t-tests were used to evaluate the effects of morphine pretreatment on brain alcohol and arterial blood alcohol levels. The statistical significance level was set at 0.05.

RESULTS

Experiment 1

Pretreatment with morphine in doses ranging from 1.5 to 4.5 g/kg SC dramatically inhibits absorption of alcohol following oral intubation (Fig. 1a). ANOVA revealed a significant effect of pretreatment [$F(3, 185) = 12.4$, $p < 0.001$] and time [$F(5, 185) = 12.4$, $p < 0.001$] as well as a treatment × time interaction [$F(15, 185) = 2.3$, $p < 0.01$], which confirms the visual observation that morphine inhibits alcohol absorption and that the effect is time and dose dependent. Post hoc Newman–Keuls tests indicated that BALs in rats treated with 1.5 and 3.0 mg/kg of morphine were essentially similar to one another ($p > 0.05$) but were significantly lower than those in rats pretreated with saline. BALs in rats pretreated with the 4.5-mg/kg dose of morphine were significantly lower ($p < 0.05$) than those in rats pretreated with saline or 1.5 or 3.0 mg/kg of morphine, indicating that the effects of morphine on alcohol absoption were dose dependent.

The effects of pretreatment with various doses of naltrexone on the absorption and elimination of alcohol (1 g/kg by oral intubation) are shown in Fig. 1b. ANOVA showed a significant effect of naltrexone pretreatment [$F(3, 185) = 4.7$, $p < 0.01$] and time [$F(5, 185) = 3.6$, $p < 0.001$], indicating that BALs vary with time following alcohol administration and that naltrexone pretreatment significantly lowers BALs. Post hoc Newman–Keuls tests revealed that all naltrexone-pretreated groups had significantly lower BALs than the saline group. There were, however, no significant differences among various naltrexone-pretreated groups ($p > 0.05$).

Experiment 2

The effects of pretreatment with morphine (3 mg/kg IP) or naltrexone (3 mg/kg IP) on the absorption of an intragastric

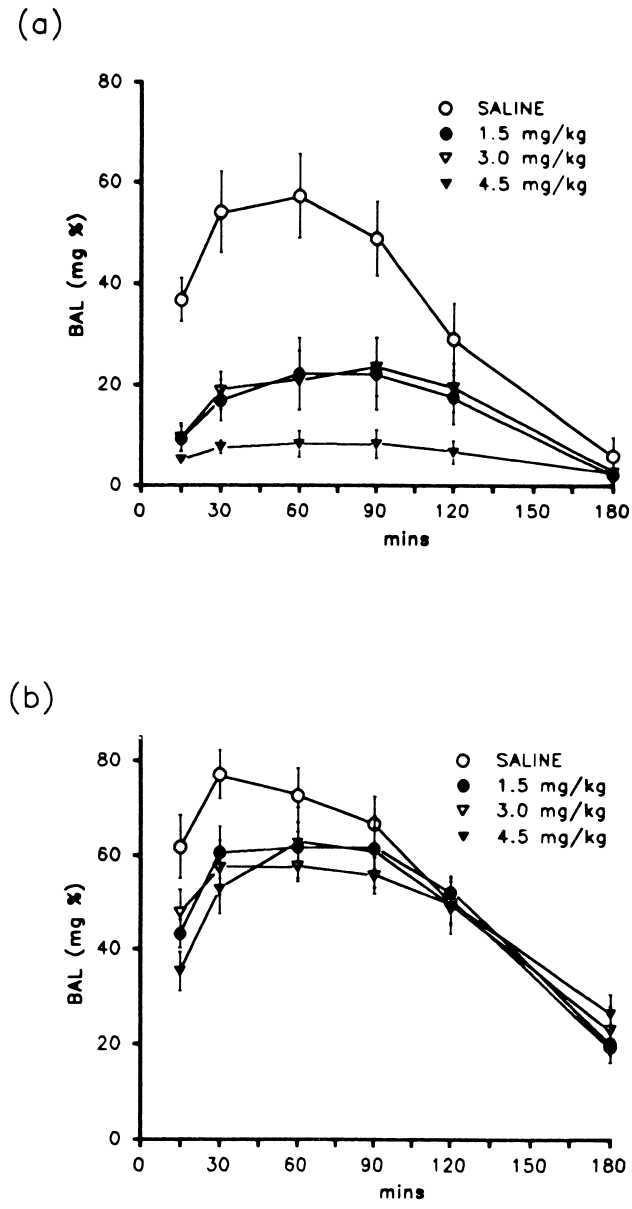

FIG. 1. Effects of pretreatment with various doses of (a) morphine and (b) naltrexone on blood alcohol levels after oral intubation with 1 g/kg of alcohol. Vertical lines through the data points, in this and subsequent figures, represent SEM. n = 8 animals per group.

infusion of 1 g/kg of alcohol are shown in Fig. 2a and b, respectively. ANOVA showed a highly significant effect of morphine pretreatment [$F(1, 200) = 51$, $p < 0.001$] and a significant time × pretreatment interaction [$F(10, 200) = 9.4$, $p < 0.001$], indicating that pretreatment with morphine inhibits the absorption of ethanol. BALs were slightly reduced during the absorptive phase in the naltrexone-pretreated group and slightly raised in the later phase (Fig. 2b). This visual observation is confirmed by ANOVA. A significant effect of naltrexone pretreatment × time [$F(10, 200) = 4.27$, $p < 0.001$] but no main effect of naltrexone pretreatment was observed.

Pretreatment with loperamide also reduced alcohol absorption in a manner similar to that of morphine (Fig. 3). There was significant effect of loperamide pretreatment [$F(1, 200) = 24.3$, $p < 0.001$] as well as a significant pretreatment × time interaction [$F(10, 220) = 13.9$, $p < 0.001$], such that the group difference was most pronounced at earlier times after infusion of alcohol.

The effects of morphine and morphine + methyl-naltrexone pretreatment on absorption of alcohol are shown in Fig. 4. There was a significant overall effect of treatment [$F(1, 14) = 7.73$, $p < 0.014$], i.e., BALs in morphine-treated rats were reduced. The overall effect of pretreatment, however, was not significant. There was a significant overall effect of time [$F(10, 24) = 52.6$, $p < 0.0011$], a significant treatment × time interaction [$F(10, 294) = 6.5$, $p < 0.001$], and a significant treatment × pretreatment interaction [$F(1, 294) = 5.7$, $p < 0.02$]. In regard to the latter, pretreatment with methyl-naltrexone slightly reduced the BALs of the saline group (as had naltrexone in experiment 1 and this experiment) but had no effect on BALs of the morphine-treated group.

Pretreatment with morphine also significantly reduced brain alcohol levels ($t = 4.65$, df = 13, $p < 0.001$) as well as arterial blood alcohol levels ($t = 3.04$, df = 13, $p < 0.01$) after alcohol administration (Fig. 5).

DISCUSSION

These experiments have shown that small doses of morphine dramatically reduce BALs attained as a result of oral administration of alcohol through either an intubation needle or an intragastric cannula. BALs demonstrate a reduced rate of absorption, reduced peak BALs, and reduced area under the curve, a pattern indicative of reduced absorption of alcohol primarily as a result of a reduced rate of stomach emptying (34). Although the entire blood alcohol curves presented are based on values obtained from tail blood, which will underestimate arterial and brain ethanol levels before equilibration within the body has taken place (20), results from the last phase of experiment 2 demonstrated that pretreatment with morphine reduced arterial blood and brain alcohol levels as well.

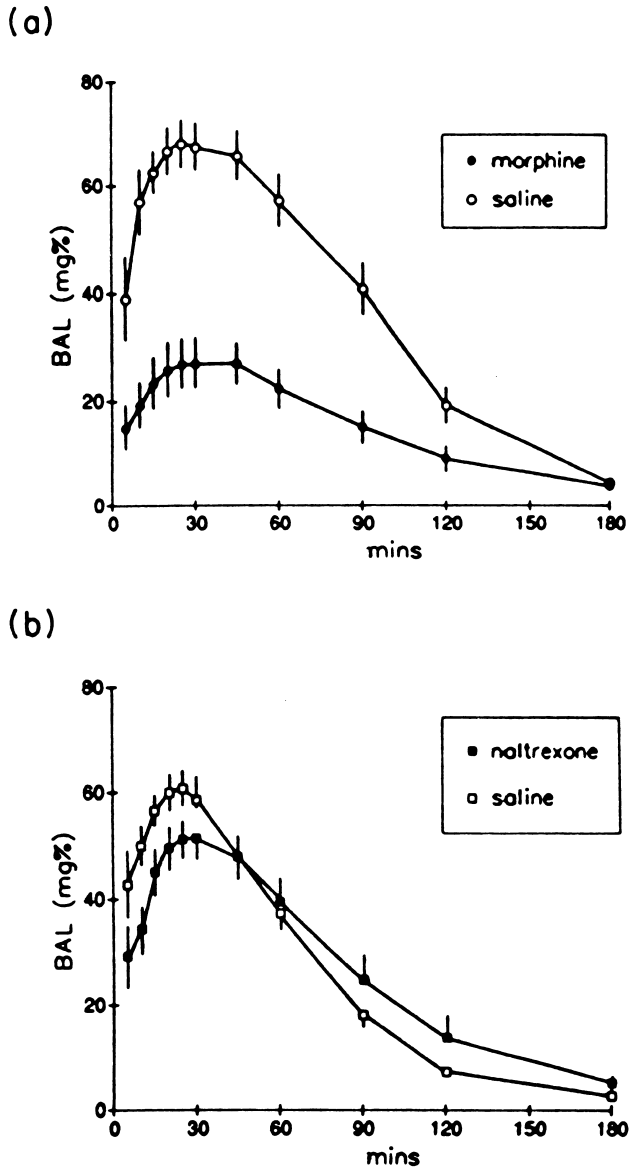

FIG. 2. Effects of pretreatment with (a) 3 mg/kg of morphine IP and (b) 3 mg/kg of naltrexone IP on blood alcohol levels after intragastric administration of 1 g/kg of alcohol. $n = 12$ animals per group.

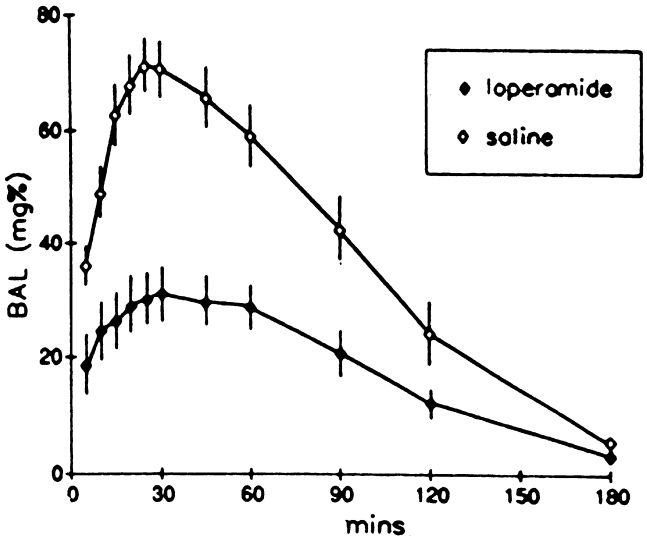

FIG. 3. Effect of 1 mg/kg of loperamide IP on blood alcohol levels after intragastric infusion of 1 g/kg of alcohol. $n = 12$ animals per group.

These results differ from those previously reported on opiate effects on BALs (6), but in that study, the alcohol was administered IP, thus bypassing the stomach, and the rate of stomach emptying may be an extremely important factor in determining the rate of absorption of alcohol following oral consumption. Hubbell et al. (9), however, also reported that rats pretreated with 1 mg/kg of morphine consumed more alcohol and attained higher BALs than did saline-pretreated rats. Although it is difficult to evaluate the effects of morphine on BALs from that study (9) due to the differences in amount of alcohol consumed between the saline- and morphine-treated groups, the results indicated that morphine pretreatment did not produce as dramatic effects on BALs as were observed in the present study. With the possible exception of the differences in the morphine dose employed (1 vs. 1.5 mg/kg) we do not have any explanation for the discrepancy between our findings and those of Hubbell et al. (9).

The effects of morphine on alcohol absorption were not modified by pretreatment with methyl-naltrexone, a peripherally acting opiate antagonist. On the other hand, loperamide, a peripherally acting opiate agonist (22), was found to decrease alcohol absorption in a manner similar to that of morphine. It has been well documented that the effects of opioids on GI motility include an inhibition of gastric emptying and intestinal transit (12,13). Such effects can be mediated peripherally and/or through a central mechanism of action on various opioid receptor types located in the GI tract and the central nervous system [see (12) for review]. The failure of methyl-naltrexone to modify the effect of morphine on alcohol absorption indicates that morphine can reduce alcohol absorption through a central mechanism. On the other hand, the effect of loperamide on alcohol absorption also supports the notion that opioids can inhibit GI motility through a direct action on opioid receptors located in the GI tract (12). Surprisingly, naltrexone and methyl-naltrexone also reduced the rate of alcohol absorption. The effects of naltrexone on alcohol absorption, however, were minimal compared with those of opioid agonists, and such effects were not dose related. The fact that methyl-naltrexone produced effects comparable to those of naltrexone indicates that such effects of opiate antagonists on alcohol absorption are likely to be mediated peripherally. It is difficult to explain these paradoxical effects of opioid agonists and antagonists on alcohol absorption. A number of studies, however, have suggested possible dual effects of opioids on GI motility (12). For example, administration of enkephalinase inhibitors has been shown to increase gastric emptying of a fatty meal in mice, and such effects can be reversed by methyl-naltrexone, indicating a peripheral site of action (16). Similarly, naloxone has also been reported to decrease antroduodenal contractility in humans (24). To address this issue, future studies should examine the effects of intraventricular injection of methyl-naltrexone or naltrexone.

Because stress has been shown to interfere with alcohol absorption (10), we attempted to minimize the possible contribution of stress by oral infusion of alcohol through an implanted intragastric cannula (experiment 2). Whether the differences in the extent of naltrexone's effects on alcohol absorption between experiments 1 and 2 might be related to differences in the level of stress involved in administration of the alcohol is not known. Clearly, however, the patterns of the effects of naltrexone and morphine on alcohol absorption were essentially similar between the two experiments. It should be pointed out that endogenous opioid systems are involved in stress responses (30,35). How pretreatment with naltrexone or morphine might interact with stress produced by procedures involved in alcohol administration and in collection of blood samples is not known.

As mentioned earlier, opiate antagonists such as naloxone or naltrexone have been shown to reduce (4,7,8,18,26), whereas morphine, depending on the doses employed, enhances (9,18,19,25,26) alcohol consumption. The purpose of these experiments was to determine if the effect of low doses of opioids on alcohol consumption, i.e., increasing it or decreasing it, might be explained by an effect on the pharmaco–kinetics of alcohol. A reduced rate of absorption could increase the rate of acquisition of acute tolerance to alcohol (14,21), and a reduced peak BAL could reduce the degree of

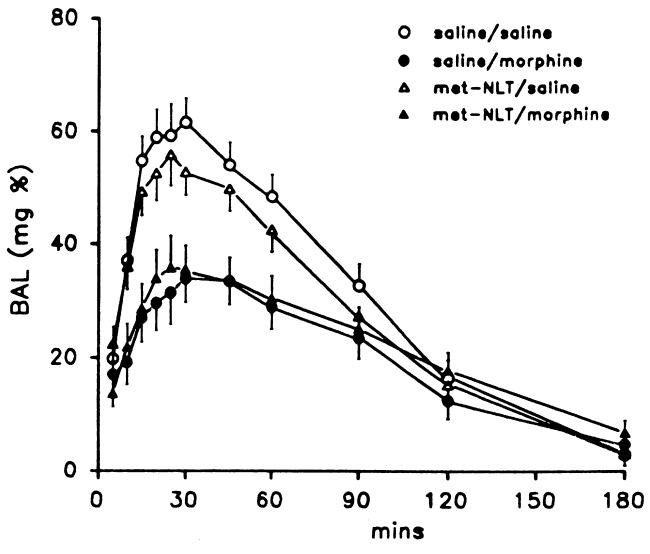

FIG. 4. Effect of methyl-naltrexone (10 mg/kg IP) blockade on the effect of morphine on blood alcohol levels after intragastric infusion of 1 g/kg of alcohol. $n = 12$ animals per group.

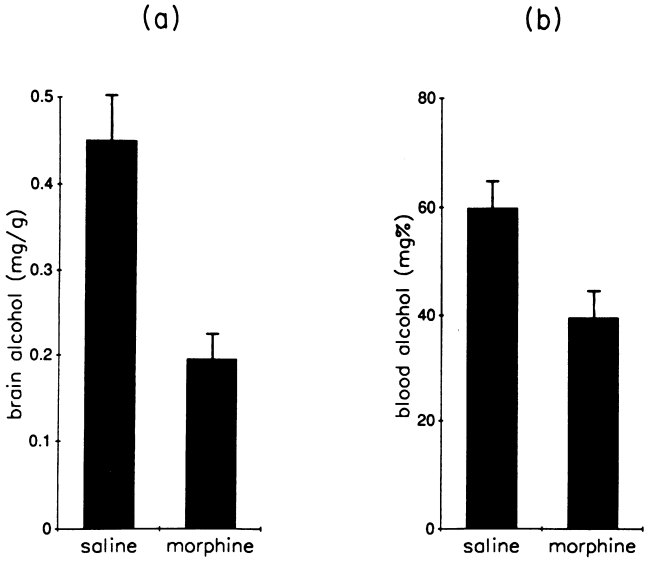

FIG. 5. Effects of 3 mg/kg of morphine IP on (a) brain and (b) arterial blood alcohol levels 7.5 min after intragastric infusion of 1 g/kg of alcohol. $n = 7$ or 8 animals per group.

intoxication produced by alcohol, both of which could increase the capacity for drinking alcohol because the signals for alcohol drinking would be postponed. Morphine and naltrexone in doses that have been found to increase and decrease alcohol consumption, respectively (18), were found to reduce alcohol absorption, although to different extents. Furthermore, loperamide, a peripherally acting opiate-like drug, also reduced alcohol absorption in a manner and extent similar to morphine, but did not have any effect on alcohol consumption (18). Together, these observations indicate that reduction in BALs is not a sufficient explanation for the modulation of alcohol consumption by opiate agonists and antagonists. It likely that the opposite effects of morphine and naltrexone on ethanol might be due to their different effects on the rewarding effects of alcohol. In this context, ethanol and morphine has been shown to stimulate dopamine release in the nucleus accumbens, an effect that has been implicated in their rewarding properties (28,32). On the other hand, naltrexone has been shown to block such effect of ethanol on dopamine release (3,33).

REFERENCES

1. Belenko, S.; Woods, S. C.: Physiological correlates of ethanol self-selection by rats. Physiol. Psychol. 1:155–157; 1973.
2. Benitez, M.; Boada, J.; Diaz, E.; Feria, M.; Prunell, M.: Naloxone-induced increase in blood and brain ethanol concentrations in rats. Pharmacol. Res. Commun. 19:723–729; 1987.
3. Benjamin, D.; Grant, E. R.; Pohorecky, L. A.: Naltrexone reverses ethanol stimulated dopamine release in the nucleus acumbens of awake, freely moving rats. Alcohol Alcohol. 27(suppl. 1):60; 1992.
4. Froehlich, J. C.; Harts, J.; Lumeng, L.; Li, T. K.: Naloxone attenuates voluntary ethanol intake in rats selectively bred for high ethanol preference. Pharmacol. Biochem. Behav. 35:385–390; 1990.
5. Haggard, H. W.; Greenberg, L. A.; Lolli, G.: The absorption of alcohol with special reference to its influence on the concentration of alcohol appearing in the blood. Q. J. Stud. Alcohol 1:684–726; 1947.
6. Ho, A. K. S.; Chen, R. C. A.: Interactions of narcotics, narcotic antagonists, and ethanol during acute, chronic and withdrawal states. Ann. N.Y. Acad. Sci. 281:297–310; 1976.
7. Hodge, C. W.; Niehus, J. S.; Samson, H. H.: Morphine induced changes in ethanol- and water-intake are attenuated by the 5-HT3/4 antagonist tropisetron (ICS 205-930). Psychopharmacology 119:186–192; 1995.
8. Hubbell, C. L.; Abelson, M. L.; Wild, K. D.; Neuman, R.; Reid, L. D.: Further studies of opioids and intake of sweetened alcoholic beverage. Alcohol 5:141–146; 1988.
9. Hubbell, C. L.; Mankes, R. F.; Reid, L. D.: A small dose of morphine leads rats to drink more alcohol and achieve higher blood alcohol concentrations. Alcohol. Clin. Exp. Res. 17:1040–1043; 1993.
10. Kalhorn, T. F.; Bowden, D. M.; Slattery, J. T.: Effects of food, mild stress, and distributed intake on the absorption and plasma concentration–time profile of orally ingested ethanol in pigtailed macaques. Pharmacol. Biochem. Behav. 24:491–496; 1986.
11. Kissileff, H. R.: Manipulation of oral and gastric environments. In: Myers, R. D., ed. Methods in psychobiology, vol. 2. Academic Press, New York; 1972:125–154.
12. Kromer, W.: Endogeneous and exogeneous opioids in the control of gastrointestinal motility and secretion. Pharmacol. Rev. 40:121–162; 1988.
13. Kromer, W.: The current status of opioid research on gastrointestinal motility. Life Sci. 44:579–589; 1989.
14. Lê;, A. D.; Khanna, J. M.: Dispositional mechanisms in drug tolerance and sensitization. In: Goudies, A. J.; Emmett-Oglesby, M., ed. Psychoactive drugs: Tolerance and sensitization. Clifton, NJ: The Humana Press; 1989:281–351.
15. LeBlanc, A. E.: Microdetermination of alcohol in blood by gas–liquid chromatography technique. Can. J. Physiol. Pharmacol. 46: 665–667; 1968.
16. Liberge, M.; Riviere, P. M.; Bueno, L.: Influence of enkephalinase inhibitors on gastric emptying in mice depends on the nature of the meal. Life Sci. 42:2047–2053; 1988.
17. Linseman, M. A.: Alcohol consumption in free-feeding rats: Procedural, genetic and pharmacokinetic factors. Psychopharmacology 92:254–261; 1987.
18. Linseman, M. A.: Central vs. peripheral mediation of opioid effects on alcohol consumption in free-feeding rats. Pharmacol. Biochem. Behav. 33:407–413; 1989.
19. Linseman, M. A.; Harding, S.: Intracerebroventricular morphine enhances alcohol consumption by rats. Pharmacol. Biochem. Behav. 30:405–408; 1990.
20. Lumeng, L.; Waller, M. B.; McBride, W. J.; Li, T. K.: Different sensitivities to ethanol in alcohol-preferring and nonpreferring rats. Pharmacol. Biochem. Behav. 16:125–130; 1982.
21. Mirsky, I. A.; Piker, P.; Rosenbaum, M.; Lederer, H.: "Adaptation" of the central nervous system to varying concentration of alcohol in the blood. Q. J. Stud. Alcohol 1:35–45; 1941.
22. Niemegeers, C. J. E.; Lenaerts, F. M.; Jansen, P. A. J.: Loperamide (R18553), a novel type of antidiarrheal agent. Part 2: In vivo parenteral pharmacology and acute toxicity in mice. Comparison with morphine, codeine and diphenoxylate. Arzneimittelforschung 24:1636–1640; 1974.
23. Porreca, F.; Galligan, J. J.; Burk, T. F.: Central opioid receptor involvement in gastrointestinal motility. Trends Pharmacol. Sci. 7:104–107; 1981.
24. Rees, W. D. W.; Sharpe, G. R.; Christofides, N. D.; Bloom, S. R.; Turnberg, L. A.: The effects of an opiate agonist and antagonist on the human upper gastrointestinal tract. Eur. J. Clin. Invest. 13:221–225; 1983.
25. Reid, L. D.; Czirr, S. A.; Bensinger, C. C.; Hubbell, C. L.; Volanth, A. J.: Morphine and diprenorphine together potentiate intake of alcoholic beverages. Alcohol 4:161–168; 1987.
26. Reid, L. D.; Hunter, G. A.: Morphine and naloxone modulate intake of ethanol. Alcohol 1:33–37; 1984.
27. Smolen, T. N.; Smolen, A.: Blood and brain ethanol concentrations during absorption and distribution in long-sleep and short-sleep mice. Alcohol 6:33–38; 1989.
28. Spanagel, R.; Herz, A.; Sippenberg, T. S.: The effects of opioid peptides on dopamine release in the nucleus accumbens: An in vivo microdialysis study. J. Neurochem. 55:1734–1739; 1990.
29. Sunahara, G. I.: Effect of ethanol on stimulated acetylcholine release in vitro from rat cortical and hippocampal tissue [M.Sc. thesis]. Toronto: University of Toronto; 1979.
30. Terman, G. W.; Shavit, Y.; Lewis, J. W.; Cannon, T. J.; Liebeskind, J. C.: Intrinsic mechanisms of pain inhibition: Activation by stress. Science 226:1270–1276; 1984.
31. Waller, M. B.; McBride, W. J.; Lumeng, L.; Li, T. K.: Effects of intravenous ethanol and of 4-methylpyrazol on alcohol drinking in alcohol-preferring rats. Pharmacol. Biochem. Behav. 17:763–768; 1982.
32. Weiss, F.; Lorang, M. T.; Bloom, F. E.; Koob, G. F.: Oral alcohol self-administration stimulates dopamine release in the rat nucleus accumbens: Genetic and motivational determinants. J. Pharmacol. Exp. Ther. 267:250–256; 1993.
33. Widdowson, P. S.; Holman, R. B.: Ethanol-induced increase in endogeneous dopamine release may involve endogeneous opiates. J. Neurochem. 59:157–163; 1992.
34. Wilkinson, P. K.: Pharmacokinetics of ethanol: A review. Alcohol. Clin. Exp. Res. 4:6–21; 1980.
35. Yamada, K.; Nabeshima, T.: Stress-induced behavioral responses and multiple opioid systems in the brain. Behav. Brain Res. 67:133–145; 1995.