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Attenuation of Alcohol Drinking in Tetrahydroisoquinoline-Treated Rats by Morphine and Naltrexone

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CRITCHER, E. C., C. I. LIN, J. PATEL AND R. D. MYERS. *Attenuation of alcohol drinking in tetrahydroisoquinoline-treated rats by morphine and naltrexone.* PHARMACOL BIOCHEM BEHAV **18**(2) 225–229, 1983.—In rats of either the Sprague-Dawley or Long-Evans strain, either tetrahydroisoquinoline (THP) was infused chronically ICV, or one of three protoberberine (PBN) compounds was administered subcutaneously at birth. When the animals were 120–180 days of age, a constant concentration of alcohol was offered simultaneously with water to those rats which demonstrated a clear-cut preference for alcohol. This concentration was selected on the basis of an alcohol preference screen. After alcohol intakes had stabilized, naltrexone was injected subcutaneously in a dose of either 1.0 or 5.0 mg/kg twice a day for three consecutive days. The higher dose (10.0 mg/kg total) of naltrexone suppressed the voluntary intake of alcohol by 26%, whereas the lower dose (2.0 mg/kg total) attenuated alcohol drinking by 14%. Both doses of naltrexone reduced food intake but did not appreciably affect water intake or body weight. When morphine was injected according to the same regimen in a dose of 10.0 or 2.5 mg/kg twice per day, a 49% reduction in alcohol intake was produced by the higher dose and a 32% decline followed the lower dose. Although morphine attenuated food intake, neither water intake nor body weight was affected. Saline control injections administered twice daily in the same way failed to alter any of the intake measures or body weight. These findings indicate that the long-lasting opiate antagonist naltrexone attenuates the voluntary consumption of alcohol in a manner similar to that produced by naloxone. The present results are discussed in terms of the evidence that an opiate agonist and antagonist may exert their actions by different mechanisms in the brain, possibly through separate subpopulations of opiate receptors.

TIQ-induced alcohol drinking Morphine Opiate receptors Opiate agonists/antagonists Naltrexone

RECENTLY, it was shown that the opiate antagonist, naloxone, attenuates the voluntary drinking of alcohol in the rat given repeated intraventricular (ICV) infusions of tetrahydropapaveroline (THP) [21]. This observation has provided further support for the viewpoint that the excessive self-administration of alcohol produced by an amine-aldehyde condensation product [22] may involve an opiate receptor mechanism in the brain [3,26]. Other evidence for such a functional relationship between alcohol and opiate mechanisms includes the findings that: (1) opioid and certain tetrahydroisoquinoline (TIQ) compounds exhibit structurally similar chemical characteristics [18]; (2) pharmacologically efficacious doses of a TIQ can produce analgesia in the rodent which is blocked by naloxone [8]; and (3) certain TIQs possess an affinity for opiate binding sites as measured by naloxone displacement in homogenate of rat brain [34,35]. That an aldehyde-condensation product could be involved in the disease state of alcoholism has received further support by the fact that salsolinol has not only been detected in the cerebrospinal fluid (CSF) but also in subcortical structures of the alcoholic patient [5,33].

In view of these findings and the fact that naloxone is a short-acting drug, the present set of experiments was designed to determine the differential effects of an opiate antagonist and agonist on the volitional drinking of alcohol produced by prior treatment with TIQs. In this study, naltrexone was selected rather than naloxone because of its longer action and because this drug reportedly suppresses the intravenous self-administration of ethanol in the monkey [1]. In addition, the opiate agonist morphine was employed following the same paradigm because of previous reports that suggested that self-selection of alcohol is affected by the systemic administration of morphine [29,32].

METHOD

Male rats of either the Sprague-Dawley (n=27) or Long-

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Evans (n=25) strain, weighing between 420 and 750 grams, were housed individually in a colony room maintained at an ambient temperature of 21 to 23°C and on a 12-hr light cycle. Each animal was given ad lib access to Wayne Lab Blox and water throughout the experiments. Measures of body weight, food and fluid intakes were taken at the same time each day.

Test of Alcohol Preference

Preference for alcohol was determined for each rat by the three-bottle, two-choice method [24]. One bottle contained water, a second contained alcohol and the third remained empty. The positions of the tubes were rotated daily to prevent the development of a position habit. The concentration of alcohol was increased systematically on each day so that a preference-aversion curve over a range of solutions from 3 to 30% (v/v) could be obtained [19].

TIQ Induction of Alcohol Drinking

One of two TIQ treatment procedures was used to induce alcohol drinking in the rat. In one set of animals, THP HBr was infused ICV either unilaterally or bilaterally on a once daily basis. An artificial CSF solution [17] containing 0.1 mg/ml of ascorbic acid to retard the degradation of THP [25] served as the carrier vehicle. The dose of the alkaloid condensation product ranged from 0.1 to 1.0 μg according to procedures described previously [23].

In the remaining rats, one of three protoberberine (PBN) compounds was injected subcutaneously in the neonatal animal along the dorsal midline of the body near the head. The injection was given during the first 24-hr postnatal period and once again 24 hr later. Each protoberberine solution was injected in a volume of 50 μl under aseptic precautions taken to prevent rejection of the rat pups by the dam. The respective doses of PBN compounds administered were selected on the basis of their toxicity (LD50) as determined by H. Bruderer (personal communication) as follows: 1.0 mg of PBN 37 (12-0637/001); 0.5 mg of PBN 35 (12-0635/001); or 25 μg of PBN 36 (12-0636/001). Each rat was then returned to its litter with no additional intervention. At 70 days of age and again at 100 days, each rat was tested for its alcohol preference as described previously.

In subsequent tests, animals were selected following TIQ treatments which drank at least 2.0 g/kg of alcohol during the preference tests. Water and a single fixed concentration of alcohol, which was ordinarily the solution of greatest intake, were offered again in the two-choice, three bottle paradigm.

Preparation and Injection of Drug Solution

Naltrexone (Endo Labs) and morphine sulfate (Mallinckrodt, Inc.) were prepared following sterile procedures in 0.9% physiological saline with pyrogen-free glassware. The drug solutions as well as the saline control solution were stored at −20°C between injections.

Naltrexone was injected in a dose of 5.0 mg/kg or 1.0 mg/kg administered twice daily. Morphine in a dose of 20.0 ng/kg or 2.5 mg/kg was injected twice a day. Each drug or an isovolumetric amount of saline was given for three days according to the injection schedule described as follows.

Following at least four days of stable baseline alcohol drinking, either the drug or saline was injected subcutaneously twice a day for three consecutive days within the three hours before or after the beginning of the light/dark cycle.

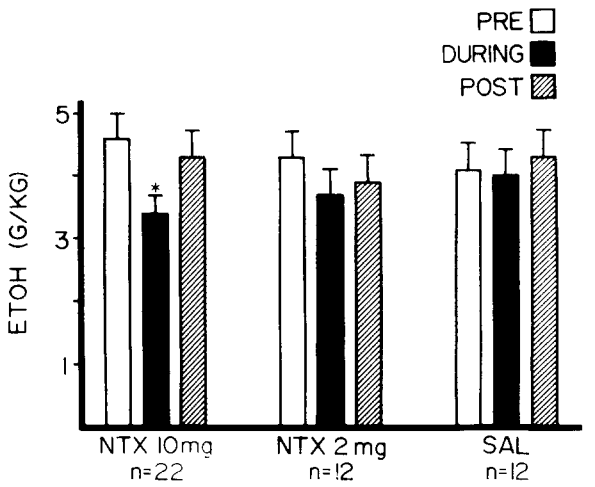

FIG. 1. Effect of naltrexone (NTX) or saline (SAL) on alcohol intake (G/KG). Bars represent the mean intake of alcohol for the four-day baseline (PRE), the three-day injection period (DURING), and the four-day period following injections (POST). Vertical lines represent standard errors. Doses are expressed as the total daily dose and n indicates the number of experiments. $^*p<0.05$.

After injections were terminated, alcohol intake was measured for at least four days or until the intake of alcohol returned to pre-injection level. A repeated measures design in which each animal received both saline and drug injections in a counterbalanced order was employed.

RESULTS

In the THP- or protoberberine-treated rat, both the opiate agonist and antagonist attenuated the voluntary consumption of alcohol. Although the ingestion of food was also suppressed by the two drugs, body weight was differentially affected. Successive injections of the control saline vehicle failed to alter any of the intake measures or body weight. The attenuation of alcohol preference by naltrexone was dose-dependent, whereas the intake of food was reduced equally by the two doses of naltrexone.

Since the mean intakes of alcohol of the Long-Evans and Sprague-Dawley strains were not statistically different either prior to ($t(20)=1.03$, $p>0.05$) or during ($t(20)=1.12$, $p>0.05$) the three-day period of injection, the data were pooled for a composite analysis. No order effects were observed when the differences in alcohol consumption were compared in those animals treated with the drug during the first or second injection sequences, $t(11)=-0.95$, $p>0.05$.

Effect of Naltrexone on Alcohol Intake

The 5.0 mg/kg dose of naltrexone injected twice daily (i.e., 10.0 mg/kg per day) reduced alcohol consumption by 26%. As illustrated in Fig. 1, the mean basal intake of alcohol of 4.6 g/kg declined significantly to 3.4 g/kg during the three successive days of the naltrexone injections, $t(21)=2.45$, $p<0.05$. During the four-day period following naltrexone treatment (POST) the intake of alcohol increased but did not reach the pre-injection baseline level.

Although the lower dose of 1.0 mg/kg of naltrexone given twice per day also suppressed alcohol drinking, this decline was not statistically significant, $t(11)=1.19$, $p>0.05$. Figure 1 shows that the mean intake of alcohol of 4.3 g/kg decreased

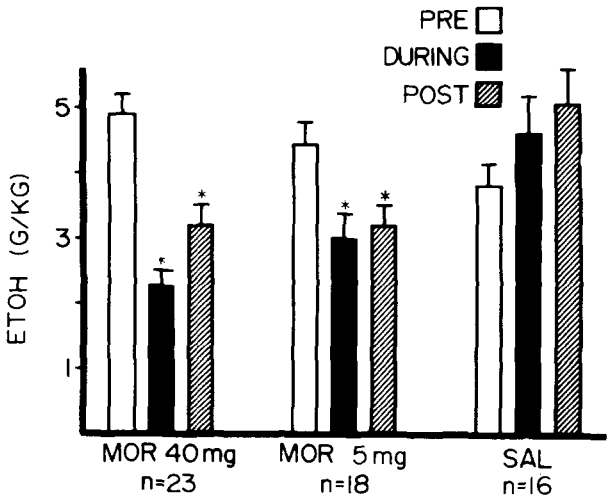

FIG. 2. Effect of morphine (MOR) or saline (SAL) on alcohol intake (G/KG). Bars represent the mean intake of alcohol for the four-day baseline (PRE), the three-day injection period (DURING), and the four-day period following injections (POST). Vertical lines represent standard errors. Doses are expressed as the total daily dose and n indicates the number of experiments. $^*p<0.01$.

to 3.7 g/kg during the injections of naltrexone, with alcohol drinking once again increasing following treatment. In contrast to the pattern of alcohol intake exhibited by the naltrexone-treated animals, the preference for alcohol in the saline-treated controls was slightly enhanced due presumably to acclimation [37].

Effect of Morphine on Alcohol Drinking

Both the 20.0 mg/kg and 2.5 mg/kg doses of morphine given twice daily significantly suppressed the voluntary consumption of alcohol below the pretreatment base-line level, $t(22)=7.15, p<0.01$ and $t(17)=3.13, p<0.01$, respectively. As presented in Fig. 2, the intake of alcohol in terms of g/kg was reduced by 49% in the animals given the 40.0 mg/kg dose and by 32% in the rats treated with 5.0 mg/kg of the agonist. Control injections of saline, on the other hand, did not substantially affect alcohol preference (Fig. 2).

In contrast to the short-term decline in alcohol intake produced by naltrexone, the consumption of alcohol during the four-day period following morphine treatment (POST) remained significantly below the base-line value. This result is portrayed also in Fig. 2. During the post-injection period, the intake of alcohol of the animals treated with 40.0 mg/kg per day remained at 34% of the pre-injection level, $t(22)=4.56, p<0.01$, whereas alcohol drinking of the rats injected with 5.0 mg/kg per day remained at 28% of the level prior to injections, $t(17)=3.03, p<0.01$.

Comparison of Naltrexone and Morphine on Food and Water Intake

The intake of food was reduced significantly by both the 10.0 and 2.0 mg/kg doses of naltrexone, $t(21)=2.85, p<0.01$ and $t(11)=2.45, p<0.05$, respectively. As shown in Table 1, a slight but insignificant decline in water intake was also produced by both naltrexone and saline; however, in both cases body weight was relatively unaffected.

Food intake declined by 50% during the treatment with morphine in a daily dose of 40.0 mg/kg. Conversely, water intake increased slightly as indicated in Table 2. In spite of the substantial reduction in total calories consumed in the form of alcohol and food during morphine injections, the body weight of the rats was unchanged. However, during the four-day period following morphine, the average body weight declined even though the mean intake of food returned to the base-line level. The 5.0 mg/kg dose of morphine reduced food intake significantly by 25%, $t(17)=4.80$, $p<0.01$, whereas water intake and body weight were not appreciably affected. However, following this injection sequence, average body weight of the animals also declined slightly.

An overall comparison of the effects of naltrexone and morphine, both given twice daily, is presented in Table 3 in terms of mean percent change in body weight and the intakes of both food and alcohol. Whereas the body weight in the case of both drugs remained stable, the baseline intakes of food and alcohol were reduced by two- to three-fold by mor-

TABLE 1

EFFECT OF NALTREXONE OR SALINE ON BODY WEIGHT AND INTAKE OF FOOD AND WATER

		Body Weight (g)	Food (g)	Water (ml)
Naltrexone	PRE	586 ± 18	22 ± 0.7	14 ± 2.4
5.0 mg 2×D	DURING	583 ± 18	*19 ± 1.0	11 ± 2.1
n=22	POST	587 ± 18	24 ± 0.9	14 ± 2.5
Naltrexone	PRE	645 ± 24	24 ± 1.2	12 ± 3.0
1.0 mg 2×D	DURING	648 ± 25	†20 ± 0.9	12 ± 2.8
n=12	POST	651 ± 25	25 ± 0.9	11 ± 3.6
Saline	PRE	630 ± 23	24 ± 0.8	11 ± 2.9
n=12	DURING	634 ± 23	24 ± 0.9	9 ± 3.0
	POST	635 ± 23	23 ± 0.7	8 ± 2.4

PRE denotes the four-day baseline, DURING the three-day injection period and POST the four days following injections. Values represent means±standard errors. $^*p<0.01$; $^†p<0.05$.

TABLE 2

EFFECT OF MORPHINE OR SALINE ON BODY WEIGHT AND INTAKE OF FOOD AND WATER

		Body Weight (g)	Food (g)	Water (ml)
Morphine	PRE	462 ±14	24 ± 1.0	12 ± 2.0
20.0 mg 2×D	DURING	462 ± 14	*12 ± 0.8	14 ± 1.9
n=23	POST	436 ± 12	23 ± 1.2	11 ± 1.4
Morphine	PRE	679 ± 23	24 ± 1.0	13 ± 2.5
2.5 mg 2×D	DURING	678 ± 22	*18 ± 0.9	14 ± 2.4
n=18	POST	671 ± 22	25 ± 1.0	13 ± 2.6
Saline	PRE	467 ± 8	24 ± 1.5	18 ± 2.7
n=16	DURING	470 ± 9	25 ± 1.3	14 ± 2.7
	POST	472 ± 8	23 ± 0.9	11 ± 1.9

PRE denotes the four-day baseline, DURING the three-day injection period and POST the four days following injections. Values represent means±standard errors. $^*p<0.01$.

TABLE 3

PERCENT CHANGE IN BODY WEIGHT AND INTAKE OF FOOD AND ALCOHOL DURING TREATMENT

		Body Weight	Food	Alcohol
Naltrexone	10.0 mg	−1%	−15%	−26%
	2.0 mg	0	−15%	−14%
Saline		+1%	− 1%	− 2%
Morphine	40.0 mg	0	−50%	−49%
	5.0 mg	0	−25%	−32%
Saline		+1%	+ 4%	+20%

Mean percent calculations are based on g for food intake and body weight and on g/kg for alcohol.

phine in comparison with naltrexone. Although morphine produced a dose-dependent decrease in alcohol and food intake, the effect of naltrexone on food intake was constant being independent of the dose injected; however, naltrexone's effect on alcohol consumption was dose-dependent.

DISCUSSION

The present findings confirm and extend earlier reports that both an opiate antagonist and agonist can suppress voluntary drinking of alcohol in a TIQ-treated rat [14,21]. As we observed previously with the administration of naloxone [21], naltrexone unexpectedly fails to enhance alcohol drinking, which could be theoretically predicted according to the viewpoint of a TIQ-opiate interaction [20]. The degree to which naltrexone suppresses alcohol drinking is nearly identical to that produced by the shorter-acting opiate antagonist, naloxone [21]. Moreover, the pattern of alcohol intake observed not only during naloxone and naltrexone injections but also after their administration is similar.

Although the effect of naloxone and naltrexone on alcohol drinking is virtually identical, their effect on food intake is dissimilar. As we reported previously, food intake over a 24-hr interval is not reduced by periodic treatment with naloxone [21], whereas both doses of naltrexone used in the present study suppress food intake. The longer-lasting action of naltrexone presumably would account for the diminution in feeding during its administration. This is also consistent with other studies which show that an opiate antagonist can suppress food intake, whereas an opiate agonist may enhance the ingestion of food [6, 7, 12, 30].

In the present study, the prototype opiate agonist, morphine, attenuated the intake of food substantially, a finding which in one sense contrasts with two previously reported findings [30,36]. However, this discrepancy may be readily explained by the different regimen of morphine administration. In our study, morphine was injected twice daily for three consecutive days, whereas in the other studies only a single injection of the agonist was administered [30,36]. That the repeated injections of a potent opiate agonist in a pharmacologically efficacious dose can produce an effect opposite to that of a single dose would be expected. In fact, an analysis of the time course of the agonist's effect reveals that a single injection of morphine in the food-satiated rat may augment food intake immediately after the injection, but will reduce feeding over a 24-hr interval [11]. Since the body weight of the rat declines following morphine treatment at the same time that food intake returns to the normal level, it is likely that an alteration in the basal metabolic rate of the animal could be produced by morphine when it is injected repeatedly.

The finding that both morphine and the two opiate antagonists suppress the voluntary intake of alcohol may be explained in one of several ways. First, it is possible that the attenuated intake of alcohol produced by naltrexone could be due to a shift in the gustatory or olfactory threshold for alcohol. A systemically given opiate antagonist reportedly can enhance the taste aversion to saccharin produced by alcohol [16] as well as alter the taste perception of the rat [13]. However, this alternative is improbable since naloxone exerts little effect on the genetic alcohol-drinking rat [21]. In addition, neither naltrexone nor naloxone alters the discriminable property of alcohol [2].

Second, the decline in alcohol intake produced by morphine, particularly if given in a high dose, could be due to a transient but general malaise accompanied by an impairment in caloric regulation [14]. In contrast to the morphine-treated rat, naloxone fails to alter either body weight or food intake during the interval when alcohol drinking is reduced [21].

Third, morphine and naltrexone may act on different sub-populations of opiate receptors [15,38]. Although the alcohol drinking induced by a TIQ is thought to be mediated by an opiate receptor mechanism [20], the sub-type of opiate receptor involved in the response has not yet been characterized. Nevertheless, naloxone not only blocks the analgesic action of a TIQ [8] but it is also a competitive inhibitor of opiate receptor binding [34,35]. The fact that naloxone reduces alcohol drinking in the rat infused ICV with THP but not in the genetically selected, high alcohol drinking animal [21] further supports the concept that different opiate receptor mechanisms could mediate the effects of morphine and naltrexone.

Although it has been shown that a TIQ can bind to opiate receptors [34,35], once again the type of opiate receptor has not yet been identified. For example, a TIQ can inhibit the contraction of the guinea pig ileum [9,27], a tissue which contains primarily μ- or morphine receptors [15]; however, since this inhibition can be blocked but not reversed by naloxone [9,27], it is conceivable that a TIQ acts either as a partial agonist or antagonist at the μ-receptor or as an agonist at an alternative opiate receptor, possibly the δ-receptor. In fact, when alcohol either is added to a brain homogenate of the rat or is administered chronically by a forced-intake procedure, a reduction of δ-receptor binding occurs in brain tissue [10,28]. Moreover, the level of leu-enkephalin, a putative ligand with a high affinity for the δ-receptor, declines in the basal ganglia of the hamster following the rodent's prolonged consumption of alcohol [4]. If the action of a TIQ in inducing alcohol drinking is mediated through δ-receptors, it is unlikely that the suppression of alcohol intake produced by naltrexone and morphine would be caused by the respective blockade or stimulation of the same receptor.

Finally, even though the present study again suggests that the alcohol drinking evoked by a TIQ may be mediated by an opiate receptor mechanism, the possibility cannot be ruled out that the suppression of alcohol consumption by an opiate antagonist could be due to a non-specific action of the drug [31].

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REFERENCES

1. Altshuler, H. L., P. E. Phillips and D. A. Feinhandler. Alteration of ethanol self-administration by naltrexone. *Life Sci* **26:** 679–688, 1980.
2. Altshuler, H. L., E. Applebaum and T. S. Shippenberg. The effects of opiate antagonists on the discriminative stimulus properties of ethanol. *Pharmacol Biochem Behav* **14:** 97–100, 1981.
3. Blum, K. *Alcohol and Opiates: Neurochemical and Behavioral Mechanisms*. New York: Academic Press, 1977.
4. Blum, K., A. H. Briggs, S. F. A. Elston, L. DeLallo, P. J. Sheridan and M. Sar. Reduced leucine-enkephalin-like immunoreactive substance in hamster basal ganglia after long-term ethanol exposure. *Science* **216:** 1425–1426, 1982.
5. Borg, S., H. Kvande, E. Magnusson and B. Sjöquist. Salsolinol and salsoline in cerebrospinal lumbar fluid of alcoholic patients. *Acta Psychiatr Scand* (Suppl) **286:** 171–177, 1980.
6. Brands, B., J. A. Thornhill, M. Hirst and C. W. Gowdey. Suppression of food intake and body weight gain by naloxone in rats. *Life Sci* **24:** 1773–1778, 1979.
7. Brown, D. R. and S. G. Holtzman. Suppression of deprivation-induced food and water intake in rats and mice by naloxone. *Pharmacol Biochem Behav* **11:** 567–573, 1979.
8. Fertel, R. H., J. E. Greenwald, R. Schwarz, L. Wong and J. Bianchine. Opiate receptor binding and analgesic effects of the tetrahydroisoquinolines salsolinol and tetrahydropapaveroline. *Res Commun Chem Pathol Pharmacol* **27:** 3–16, 1980.
9. Hamilton, M. G., M. Hirst and K. Blum. Opiate-like activity of salsolinol on the electrically stimulated guinea pig ileum. *Life Sci* **25:** 2205–2210, 1979.
10. Hiller, J. M., L. M. Angel and E. J. Simon. Multiple opiate receptors: alcohol selectively inhibits binding to delta receptors. *Science* **214:** 468–469, 1981.
11. Kumar, R., E. Mitchell and I. P. Stolerman. Disturbed patterns of behaviour in morphine tolerant and abstinent rats. *Br J Pharmacol* **42:** 473–484, 1971.
12. Lang, I. M., J. C. Strahlendorf, H. K. Strahlendorf, L. O. Lutherer and C. D. Barnes. The effects of chronic administration of naltrexone on appetite and water exchange in rats. *Pharmacol Biochem Behav* **16:** 909–913, 1982.
13. Levine, A. S., S. S. Murray, J. Kneip, M. Grace and J. E. Morley. Flavor enhances the antidipsogenic effect of naloxone. *Physiol Behav* **28:** 23–25, 1982.
14. Lin, C. I. and R. D. Myers. Reversal of THP-induced alcohol drinking in the rat by systemic naloxone and morphine. *Alcoholism: Clin Exp Res* **2:** 188, 1978.
15. Lord, J. A. H., A. A. Waterfield, J. Hughes and H. W. Kosterlitz. Endogenous opioid peptides: multiple agonists and receptors. *Nature* **267:** 495–499, 1977.
16. Miceli, D., P. Marfaing-Jallat and J. LeMagnen. Non-specific enhancement of ethanol-induced taste aversion by naloxone. *Pharmacol Biochem Behav* **11:** 391–394, 1979.
17. Myers, R. D. General laboratory procedures. In: *Methods of Psychobiology*, vol. 1, edited by R. D. Myers. London: Academic Press, 1971, pp. 27–65.
18. Myers, R. D. Tetrahydroisoquinolines in the brain: the basis of an animal model of alcoholism. *Alcoholism: Clin Exp Res* **2:** 145–154, 1978.
19. Myers, R. D. Psychopharmacology of alcohol. In: *Annu Rev Pharmacol Toxicol* **18:** 125–144, 1978.
20. Myers, R. D. Pharmacological effects of amine-aldehyde condensation products. In: *Alcohol Tolerance and Dependence*, edited by H. Rigter and J. Crabbe. Amsterdam: Elsevier/North-Holland Biomedical Press, 1980, pp. 339–370.
21. Myers, R. D. and E. C. Critcher. Naloxone alters alcohol drinking induced in the rat by tetrahydropapaveroline (THP) infused ICV. *Pharmacol Biochem Behav* **16:** 827–836, 1982.
22. Myers, R. D. and C. L. Melchior. Alcohol drinking: Abnormal intake caused by tetrahydropapaveroline in the brain. *Science* **196:** 554–556, 1977.
23. Myers, R. D. and M. Oblinger. Alcohol drinking in the rat induced by acute intracerebral infusion of two tetrahydroisoquinolines and a β-carboline. *J Drug Alcohol Depend* **2:** 469–483, 1977.
24. Myers, R. D. and W. L. Veale. The determinants of alcohol preference in animals. In: *The Biology of Alcoholism*, vol. 2, edited by B. Kissin and H. Begleiter. New York: Plenum Press, 1972, pp. 131–168.
25. Myers, R. D., J. L. Garrison and E. C. Critcher. Degradation characteristics of two tetrahydroisoquinolines at room and body temperatures: HPLC determination with electrochemical detection. *J Liquid Chromatogr*, in press, 1982.
26. Nichols, J. R. and S. Hsiao. Addiction liability of albino rats: breeding for quantitative differences in morphine drinking. *Science* **177:** 561–563, 1967.
27. North, R. A., M. A. Collins, J. D. Milner, P. J. Karras and D. J. Koziol. Tetrahydroisoquinolines (TIQs) do not act on opiate receptors in the guinea-pig ileum. *Eur J Pharmacol* **71:** 489–493, 1981.
28. Pfeiffer, A., B. R. Seizinger and A. Herz. Chronic ethanol imbibition interferes with δ-, but not with μ-opiate receptors. *Neuropharmacology* **20:** 1229–1232, 1981.
29. Ross, D., R. J. Hartmann and I. Geller. Ethanol preference in the hamster: effects of morphine sulfate and naltrexone, a long-acting morphine antagonist. *Proc West Pharmacol Soc* **19:** 326–330, 1976.
30. Sanger, D. J. Endorphinergic mechanisms in the control of food and water intake. *Appetite: J Intake Res* **2:** 193–208, 1981.
31. Sawynok, J., C. Pinsky and F. S. LaBella. Minireview on the specificity of naloxone as an opiate antagonist. *Life Sci* **25:** 1621–1632, 1979.
32. Sinclair, J. D., J. Adkins and S. Walker. Morphine-induced suppression of voluntary alcohol drinking in rats. *Nature* **246:** 425–427, 1973.
33. Sjöquist, B., A. Eriksson and B. Winblad. Salsolinol and catecholamines in human brain and their relation to alcoholism. *Prog Clin Biol Res* **90:** 57–68, 1982.
34. Tampier, L., H. S. Alpers and V. E. Davis. Influence of catecholamine-derived alkaloids and β-adrenergic blocking agents on stereospecific binding of ^{3}H-naloxone. *Res Commun Chem Pathol Pharmacol* **17:** 731–734, 1977.
35. Terenius, L. Opioid peptides and opiates differ in receptor selectivity. *Psychoneuroendocrinology* **2:** 53–58, 1977.
36. Thornhill, J. A., M. Hirst and C. W. Gowdey. Disruption of diurnal feeding patterns of rats by heroin. *Pharmacol Biochem Behav* **4:** 129–135, 1976.
37. Veale, W. L. and R. D. Myers. Increased alcohol preference in rats following repeated exposures to alcohol. *Psychopharmacology* **15:** 361–372, 1969.
38. Wood, P. L. Multiple opiate receptors: support for unique mu, delta and kappa sites. *Neuropharmacology* **21:** 487–497, 1982.