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# The effect of baclofen alone and in combination with naltrexone on ethanol consumption in the rat

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**Abstract**

Naltrexone has been evaluated in preclinical animal models of ethanol consumption and found to be effective in most reports. In clinical use, naltrexone has not proved to be as efficacious in preventing relapse. While naltrexone targets opioid receptors, many other neurotransmitter systems are targeted by ethanol and, to a greater or lesser extent, contribute to modulating ethanol's reinforcing effects. There has been indication that drugs active at the gamma amino butyric acid B ($GABA_B$) receptors can affect the self-administration of many drugs with abuse potential. The experiments reported here evaluated the effect of three doses of baclofen (2.5, 5.0, or 7.5 mg/kg), a $GABA_B$ agonist, administered alone or in combination with a single dose of naltrexone (1.0 mg/kg). In Experiment 1, both naltrexone and baclofen, at the two higher doses tested, significantly reduced ethanol consumption in Wistar rats using a limited access procedure on Drug Days 1 and 2. When combined on Drug Days 3 and 4, baclofen/naltrexone was significantly more effective in reducing ethanol consumption than did either drug alone. Neither drug, alone or in combination, had an effect on water consumption. In Experiment 2, both baclofen and naltrexone again significantly reduced ethanol consumption, with no evidence that chronic administration across Drug Days 3 and 4 further reduced consumption compared with Drug Days 1 and 2. The clinical use of multiple pharmacotherapeutic agents in combination may allow for the use of lower doses of individual components, thereby reducing the negative side effects that contribute to lower compliance and higher relapse.


*Keywords:* Ethanol; Baclofen; Naltrexone; Rats

## 1. Introduction

Alcohol abuse and addiction remain a serious problem. Naltrexone, a nonselective opioid antagonist, was approved as an adjunctive pharmacotherapy for use in recovering alcoholics by the FDA in 1995. While effective in some individuals, it has not been found to be universally effective (e.g., Krystal et al., 2001). The exact mechanism of naltrexone's effect on ethanol consumption remains unclear. However, it is hypothesized that it, in some way, disrupts those neural pathways that modulate ethanol's positive reinforcing properties. Ethanol, like most drugs with abuse potential, is hypothesized to produce its reinforcing effects through the activation of the mesolimbic dopamine (DA) system (Koob, 1992). Ethanol has been demonstrated to increase extracellular levels of DA in the mesolimbic system (DiChiara and Imperato, 1985; Gonzales and Weiss, 1998; Heidbreder and De Witte, 1993; Imperato and DiChiara, 1986; Weiss et al., 1993; Yoshimoto et al., 1991) and increase the firing rate of ventral tegmental area (VTA) DA neurons (Brodie et al., 1990; Criado et al., 1995; Gessa et al., 1985). Naltrexone has been shown to attenuate the increase in DA produced by ethanol locally administered to the nucleus accumbens (Nacc; Benjamin et al., 1993) and following an initial paradoxical conditioned increase in the Nacc DA to reduce both oral ethanol self-administration and DA (Gonzales and Weiss, 1998). While naltrexone remains an effective pharmacotherapy in a subset of the population, the overall results suggest that the development of alternative pharmacotherapies, used either alone or in combination with naltrexone, will prove useful.

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One strategy utilized to identify potential pharmacotherapeutic agents is to examine those drugs that target receptor systems that either directly or indirectly modulate those mesolimbic pathways hypothesized to underlie ethanol's positive reinforcing effects. One neural system that interacts with ethanol and modulates activity in the mesolimbic DA system is gamma amino butyric acid (GABA). For example, there are three distinct GABAergic sources innervating A10 dopamine cell bodies in the VTA (Churchill et al., 1992; Kalivas et al., 1990). Research in our laboratory has reported that gamma vinyl GABA (GVG), a suicide inhibitor of GABA transaminase and an indirect GABA agonist, dose dependently reduced both oral ethanol and cocaine consumption, but not water, when all three fluids were concurrently available (Stromberg et al., 2001). Separate evidence has shown that GVG inhibits the release of extracellular DA in the Nacc during the administration of ethanol (Gerasimov et al., 1999). However, data from other experiments examining the effects of agonists and antagonists selective for GABA receptor subtypes on ethanol consumption have been mixed.

$GABA_A$ receptors have been implicated in both the acquisition and maintenance of ethanol self-administration in rats. Peripheral administration of THIP, a $GABA_A$ agonist, increased the consumption of ethanol across 24 h of continuous access, while picrotoxin, a $GABA_A$ antagonist, reduced ethanol consumption (Boyle et al., 1993). Muscimol, another $GABA_A$ agonist, injected directly into the VTA failed to produce an effect on ethanol consumption (Hodge et al., 1996). In other experiments, muscimol injected into the medial prefrontal cortex was effective in reducing ethanol self-administration at a low dose but not at higher doses (Samson and Chappell, 2001a), while being effective only at the highest dose when injected into the pedunculopontine tegmental nucleus (Samson and Chappell, 2001b). However, when injected into the Nacc, muscimol decreased both responding for and consumption of ethanol, as did the $GABA_A$ antagonist, bicuculline, at the highest dose tested (Hodge et al., 1995). In another experiment, muscimol injected into the amygdala of ethanol-dependent, but not nondependent, rats reduced responding for ethanol (Roberts et al., 1996). In nondependent rats, the $GABA_A$ antagonist, SR95531, injected into the amygdala at low doses, and at higher doses into the bed nucleus stria terminalis and shell of the Nacc, reduced responding for ethanol (Hyytia and Koob, 1995). Muscimol injected into the dorsal raphe (Tomkins et al., 1994) increased ethanol consumption. Baclofen, a $GABA_B$ agonist, has been demonstrated to increase (Petry, 1997; Smith et al., 1999), decrease (Daoust et al., 1987), or have no effect on ethanol consumption (Tomkins and Fletcher, 1996). Recently, it was reported that baclofen reduced ethanol consumption in a dose-dependent manner in ethanol-preferring sP rats (Colombo et al., 2001). In addition, in a small pilot clinical study, baclofen was shown to significantly reduce craving for alcohol (Addolorato et al., 2001).

Pharmacotherapy for many diseases, such as hypertension and diabetes, utilizes multiple drugs that act on different receptor targets. For alcoholism, this approach is limited because pharmacotherapeutic alternatives are not available. Some work has demonstrated that the use of drug combination therapy has advantages over the use of a single drug (Farren et al., 1997; Rezvani et al., 2000; Salloum et al., 1998; Williams and Mason, 1997). The experiments reported here were designed to examine the effect of a single dose of naltrexone and three doses of baclofen, administered either alone or in combination, on the consumption of ethanol in a limited access procedure using Wistar rats.

## 2. Methods

### 2.1. Subjects

Forty-eight male Wistar rats were purchased from Harlan and arrived at the laboratory weighing between 225 and 249 g. The rats were housed in individual acrylic cages in a temperature-controlled (22 °C) animal colony on a 12:12-h reverse light/dark cycle, with lights out from 0730 to 1930 h. The animals were provided with ad lib food and water for the entire experiment. All research was approved by the Institutional Animal Care and Use Committee at the Philadelphia VAMC and was conducted according to The Guide for the Care and Use of Laboratory Animals as adopted by the National Institutes of Health, (Institute of Laboratory Animal Resources, 1996).

### 2.2. Procedure

Rats were initially exposed to continuous ethanol in ascending concentrations from 2% to 8% v/v. When drinking was stable at 8%, the rats were shifted to a 1-h limited access procedure, with ethanol available between 1100 and 1200 h. Once ethanol consumption stabilized across the limited access period (defined as no change in consumption >20% across five consecutive days), the animals were injected with saline 30 min before the limited access session. The rats were matched for ethanol consumption and were randomly assigned to one of six groups, BAC2.5 + NTX1.0 ($n = 8$), BAC5.0 + NTX1.0 ($n = 8$), BAC7.5 + NTX1.0 ($n = 8$), NTX1.0 + BAC2.5 ($n = 8$), NTX1.0 + BAC5.0 ($n = 8$), or NTX1.0 + BAC7.5 ($n = 8$). Animals in each of these groups were given exposure to either naltrexone or baclofen alone for 2 days and then both drugs in combination for 2 days. Following drug administration, the animals were returned to baseline.

### 2.3. Drug

Naltrexone and baclofen were purchased from Sigma, St. Louis, MO. Naltrexone was dissolved in saline and injected intraperitoneally in a dose of 1.0 mg/kg. Baclofen

was dissolved in saline and injected intraperitoneally in doses of 2.5, 5.0, and 7.5 mg/kg. Both drug and saline control injections were administered intraperitoneally 30 min prior to the limited access period in a volume of 1.0 ml/kg.

## 3. Results

The first question asked by the present experiments was would baclofen reduce ethanol consumption comparable with naltrexone in the limited access model employed in our laboratory. The results demonstrated that baclofen, at one of the dose levels tested, and naltrexone reduced ethanol consumption across the first two drug days when they were administered alone. Fig. 1 shows ethanol consumption for all drug groups across the predrug saline day, the four drug days, and the postdrug baseline day. A two-way repeated-measures ANOVA (drug treatment, baclofen or naltrexone, repeated across predrug saline and the mean of Drug Days 1 and 2 collapsed) revealed a significant effect for days [$F(1,46) = 30.231$, $P < .001$]. Subsequent pairwise comparisons revealed that only baclofen 5.0 mg/kg significantly reduced ethanol consumption compared with ethanol consumption following saline, while naltrexone in all three groups significantly reduced ethanol consumption compared with ethanol consumption following saline.

The second question asked in these experiments was would there be an additive effect from the combination of naltrexone and baclofen on ethanol consumption. A two-way repeated-measures ANOVA (six drug treatment conditions repeated across the collapsed mean of Drug Days 1 and 2 and Drug Days 3 and 4) revealed a significant effect for days [$F(1,42) = 47.524$, $P < .001$]. Simple effects tests for the three baclofen-first and three naltrexone-first groups alone repeated across the collapsed mean of Drug Days 1 and 2 and Drug Days 3 and 4 were significant for days. Pairwise comparisons for each of the groups revealed that the combination of baclofen and naltrexone was significantly more effective at reducing ethanol consumption compared with either drug alone for four of the six groups as follows: baclofen 2.5 + Ntx 1, baclofen, baclofen 5 + Ntx 1, Ntx 1 + baclofen 2.5, and Ntx 1 + baclofen 7.5. A test for order of drug administration, baclofen or naltrexone alone, for Drug Days 1 and 2 was not significant for the drug combination on Days 3 and 4.

Fig. 2, panel A, shows the consumption of water during the 1-h limited access period. A two-way repeated-measures ANOVA (six drug treatment conditions repeated across saline and the collapsed mean of the sum of Drug Days 1

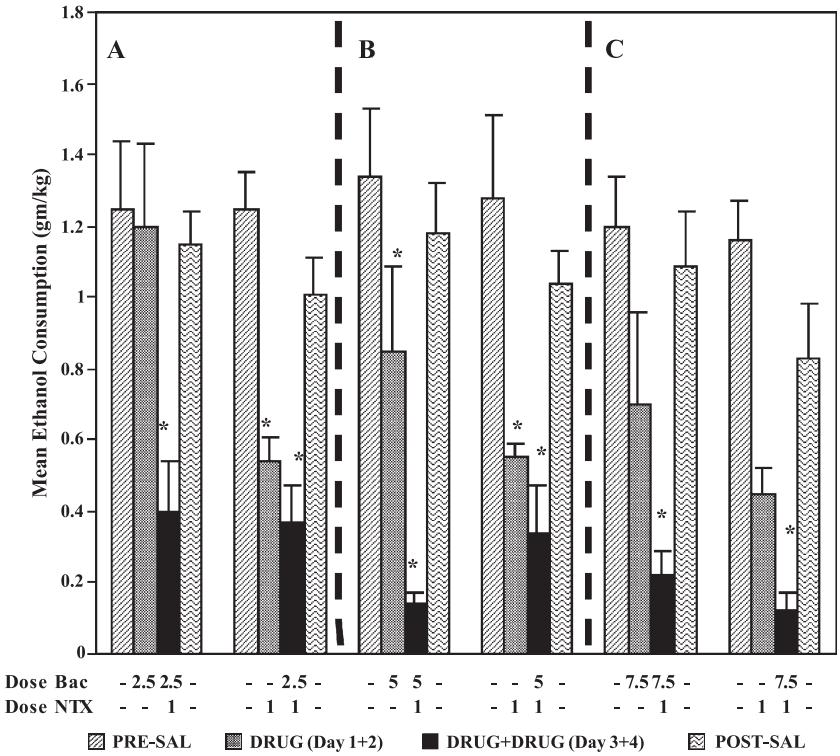


Fig. 1. (A) Effect of pre- and postdrug vehicle and baclofen 2.5 mg/kg or naltrexone 1.0 mg/kg ( ± S.E.M.) alone (Drug Days 1 and 2) or in combination (Drug Days 3 and 4). (B) Effect of pre- and postdrug vehicle and baclofen 5.0 mg/kg or naltrexone 1.0 mg/kg ( ± S.E.M.) alone (Drug Days 1 and 2) or in combination (Drug Days 3 and 4). (C) Effect of pre- and postdrug vehicle and baclofen 7.5 mg/kg or naltrexone 1.0 mg/kg ( ± S.E.M.) alone (Drug Days 1 and 2) or in combination (Drug Days 3 and 4). The dose of baclofen (Bac) or naltrexone (NTX) or no drug ( – ) is indicated on the abscissa below each column. Each value includes S.E.M. * $P < .05$.

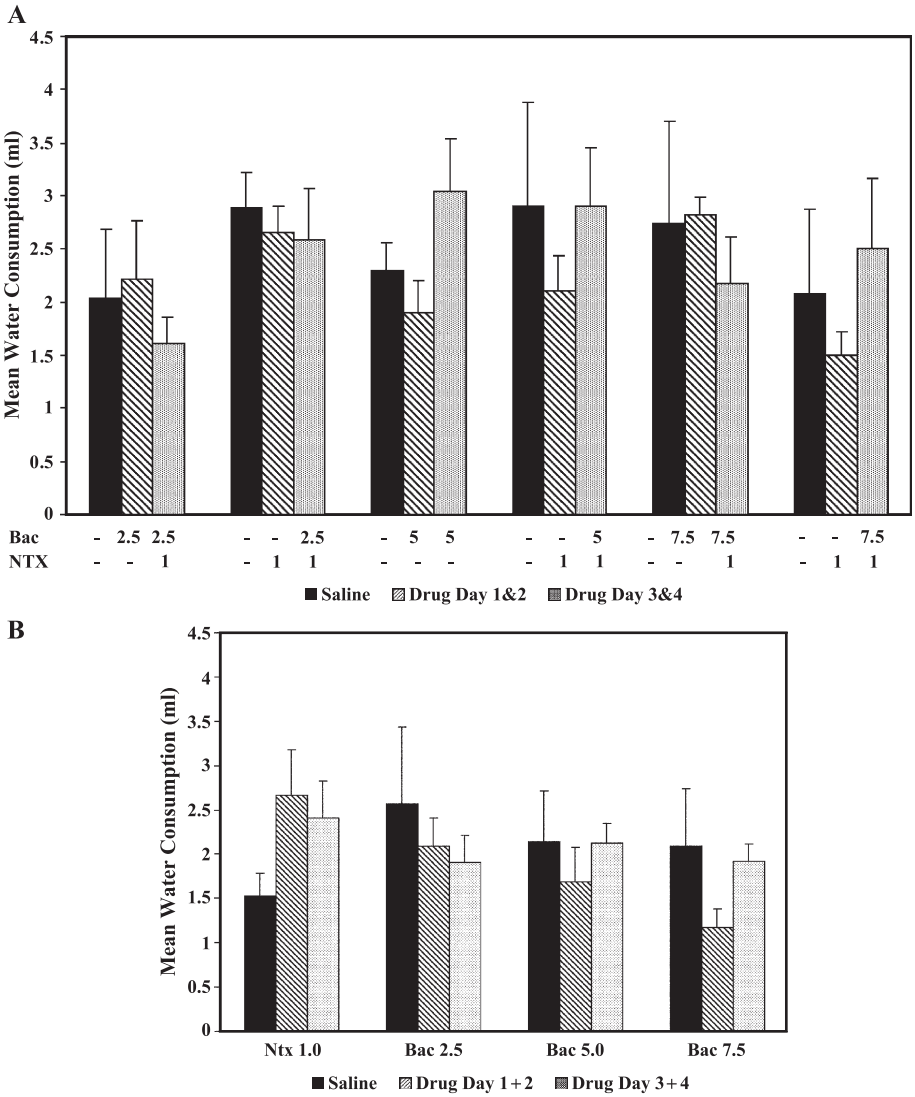


Fig. 2. (A) Effect of baclofen 2.5, 5.0, and 7.5 mg/kg alone and in combination with naltrexone 1.0 mg/kg ( ± S.E.M.) on water consumption during limited access in Experiment 1. The dose of baclofen (Bac), or naltrexone (NTX), or no drug ( − ) is indicated on the abscissa below each column. (B) Effect of baclofen 2.5, 5.0, and 7.5 mg/kg and naltrexone 1.0 mg/kg alone on ethanol consumption in Experiment 2.

and 2 and Drug Days 3 and 4) produced no significant effects.

## 4. Experiment 2

While the results of Experiment 1 suggested that the combination of baclofen and naltrexone administered on Days 3 and 4 significantly attenuated ethanol consumption compared with either drug administered alone on Drug Days 1 and 2, it is possible that the chronic effect of baclofen or naltrexone across Days 3 and 4 was responsible for the greater decrease in ethanol consumption and was unrelated to the drug combination. To examine this possibility, this experiment was designed to test the effect of baclofen, 2.5, 5.0, and 7.5 mg/kg, and naltrexone, 1.0 mg/kg, on ethanol consumption across four consecutive days.

### *4.1. Methods*

#### *4.1.1. Subjects*

Thirty-two male Wistar rats were purchased from Harlan and arrived at the laboratory weighing between 225 and 249 g. The rats were treated the same as those in Experiment 1.

#### *4.1.2. Procedure*

Rats were trained similarly to those in Experiment 1, and after consumption stabilized across the limited access period, the animals were matched for consumption and randomly assigned to one of four groups: BAC2.5

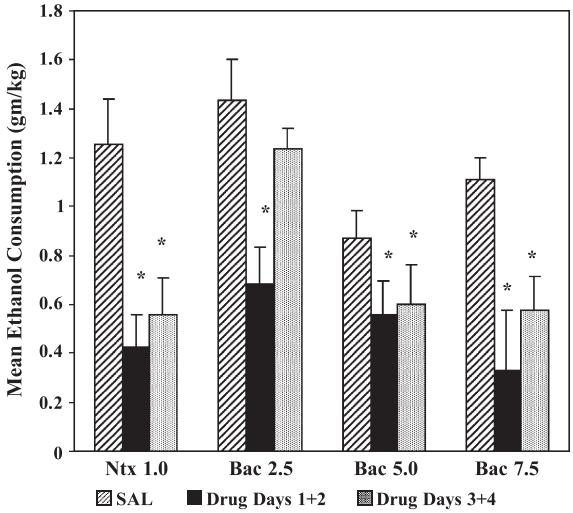


Fig. 3. Effect of saline or naltrexone 1.0 mg/kg and baclofen 2.5, 5.0, or 7.5 mg/kg ( ± S.E.M.) on ethanol consumption on predrug vehicle day or Drug Days 1 and 2 or 3 and 4 in Experiment 2. * $P < .05$.

($n = 8$), BAC5.0 ($n = 8$), BAC7.5 ($n = 8$), and NTX1.0 ($n = 8$). Animals in each of these groups were injected with saline and then either baclofen, 2.5, 5.0, or 7.5 mg/kg ip, or naltrexone, 1.0 mg/kg, alone for 4 days. Following drug administration, the animals were returned to baseline.

*4.1.3. Results*

The question being asked in this experiment was whether chronic administration of either baclofen or naltrexone across 4 days was responsible for the enhanced suppression of ethanol consumption on Days 3 and 4 when compared with Days 1 and 2 in Experiment 1. Fig. 3 shows the mean ethanol consumption across the predrug saline day and the collapsed means of Drug Days 1 and 2 and 3 and 4. An examination of these data shows that while each drug reduced ethanol consumption relative to that same consumption following saline, ethanol consumption increased on Drug Days 3 and 4 compared with on Drug Days 1 and 2. A two-way repeated-measures ANOVA (drug treatment, baclofen or naltrexone, repeated across predrug saline and the mean of Drug Days 1 and 2 collapsed) revealed a significant effect for drug treatment [$F(3,28) = 3.258$, $P = .03$] and for days [$F(1,28) = 58279$, $P < .001$]. Pairwise comparisons revealed that naltrexone 1.0 mg/kg and baclofen 5.0 and 7.5 mg/kg but not baclofen 2.5 mg/kg significantly reduced ethanol consumption compared with ethanol consumption following saline. These results are comparable with those in Experiment 1 for Drug Days 1 and 2, when all drugs were administered alone and significantly reduced ethanol consumption relative to saline. A two-way ANOVA (drug treatment, baclofen dose or naltrexone, repeated across the collapsed mean of Drug Days 1 and 1 and Drug Days 3 and 4) yielded a significant effect for drug treatment [$F(3,28) = 4.230$, $P = .014$] and for days [$F(1, 28) = 10.228$, $P = .003$]. Subsequent pairwise comparisons revealed that the only significant difference was an increase in ethanol consumption for those rats receiving baclofen 2.5 mg/kg.

Fig. 2 shows the consumption of water during the 1-h limited access period. A two-way repeated-measures ANOVA (four drug treatment conditions repeated across saline and the collapsed mean of the sum of Drug Days 1 and 2 and Drug Days 3 and 4) produced no significant effects.

## 5. Discussion

The purpose of these experiments was to investigate the effects of baclofen administered alone and in combination with naltrexone on the consumption of ethanol in a limited access model. The results for naltrexone in both Experiments 1 and 2 were consistent with other experiments done in this laboratory with a similar dose (Stromberg et al., 1998, 2002). Baclofen, administered alone, reduced ethanol consumption in a dose-dependent manner during Days 1 and 2 in Experiment 1. However, this difference was significant only for baclofen 5.0 mg/kg. Again, in Experiment 2, baclofen, administered alone, reduced alcohol consumption in a dose-dependent manner, with significant reductions compared with saline at each dose level. In Experiment 1, the combination of naltrexone and baclofen in four of the six groups reduced ethanol consumption significantly more than did either drug administered alone, suggesting an additive relationship from the drug combination. Neither drug disrupted water consumption during the limited access period, suggesting that these drugs are selective for mechanisms modulating ethanol consumption.

Previous work in our laboratory has demonstrated that GVG, a suicide inhibitor of GABA transaminase and indirect GABA agonist, decreased oral ethanol consumption when it was concurrently available with oral cocaine and water (Stromberg et al., 2001). Other research has demonstrated that this effect may be due to GVG's inhibition of ethanol-induced DA release in the Nacc (Gerasimov et al., 1999). DA release in this pathway is hypothesized to be critical for the positive reinforcing properties of drugs with abuse potential (Koob, 1992). While GVG is not selective for GABA receptor subtype, it has been hypothesized that its effect is a result of its activity at the $GABA_B$ receptor subtype (Ashby et al., 1999). GABA receptors in the VTA are thought to be important in modulating mesolimbic DA activity. In the VTA, $GABA_B$ receptors are located on the cell bodies of DA neurons, while $GABA_A$ receptors are primarily located on intrinsic interneurons (Churchill et al., 1992). However, some $GABA_A$ receptors may also be colocalized with $GABA_B$ receptors on VTA dopamine cell

bodies (Xi and Stein, 1999). The activation of these two GABA receptor subtypes appears to have a bidirectional effect on activity in the mesolimbic DA pathway. The activation of $GABA_B$ receptors in the VTA by baclofen reduces extracellular DA in the Nacc (Kalivas et al., 1990; Klitenick et al., 1992), while the activation of $GABA_A$ receptors by muscimol, a $GABA_A$ agonist, increases extracellular DA in the Nacc (Xi and Stein, 2002). While the activation of $GABA_A$ receptors is believed to increase DA activity, it has been proposed that the action of $GABA_A$ results from the summation of its disinhibitory effects on DA arising from the activation of interneurons and its inhibitory effects on DA emanating from receptors located on DA cell bodies (Xi and Stein, 1999).

At the level of behavior, baclofen has been demonstrated to reduce self-administration of cocaine (Brebner et al., 2002), heroin (Xi and Stein, 2002), nicotine (Corrigall et al., 2001), and ethanol (Colombo et al., 2001) and to reduce enhanced locomotor effects produced by cocaine and amphetamine (Kalivas et al., 1990), morphine (Woo et al., 2001), and ethanol (Chester and Cunningham, 1999). These data are consistent with the results from the experiments reported here. In Experiment 1, baclofen, 2.5, 5.0, and 7.5 mg/kg, was administered alone for 2 days before being combined with naltrexone. When administered alone, baclofen reduced ethanol consumption in a dose-dependent manner, with significant reduction at the two highest doses. In Experiment 2, using the same three doses, baclofen was administered alone across a 4-day period and had similar effects on ethanol consumption.

In both Experiments 1 and 2, naltrexone 1.0 mg/kg, a nonselective opioid antagonist, produced a significant reduction in ethanol consumption comparable with previous work in this laboratory (Stromberg et al., 1998, 2002). The precise mechanism underlying naltrexone's effect is not fully understood, but it is hypothesized that it may function by modulating ethanol's effects on mesolimbic DA pathways. There is ample evidence that ethanol produces an effect on this system and that disruption of the system disrupts ethanol consumption. For example, both experimenter-administered (DiChiara and Imperato, 1985; Wozniak et al., 1991; Yoshimoto et al., 1991; Mocsary and Bradberry, 1996; Yim et al., 1998) and orally self-administered ethanol (Weiss et al., 1993; Gonzales and Weiss, 1998) increase DA in the Nacc. Additionally, animals will self-administer ethanol directly into the VTA (Gatto et al., 1994; Rodd-Henricks et al., 2000). Other evidence comes from physiological studies showing dose-dependent increases in the firing rate of VTA dopamine neurons following the application of ethanol (Brodie et al., 1990; Criado et al., 1995; Gessa et al., 1985), while ethanol injected directly into the VTA increases extracellular DA in the Nacc (Yoshimoto et al., 1991). One study found that systemically administered ethanol increased extracellular DA in the Nacc of awake, but not anesthetized, rats (Samson et al., 1997). These authors suggest that ethanol's effects on extracellular DA in the Nacc may originate indirectly through its action in the VTA. This view is supported by data showing that ethanol administered directly into the Nacc increases extracellular DA, but only at very high doses (Wozniak et al., 1991; Yim et al., 1998).

The most interesting results of the present study are that baclofen, in combination with naltrexone, produced a reduction in ethanol consumption that was significantly greater than either drug administered alone. This effect appeared to be selective to ethanol consumption and not a result of a general suppression of either motor or appetitive behavior, as there was no change in water consumption during the limited access period. It could be argued that this effect was not due to the combination of the two drugs but rather to an effect of chronic exposure. Perhaps, the additional exposure to baclofen across Days 3 and 4, in some fashion, produced the greater decrement in ethanol consumption. This seems unlikely for two reasons. First, comparable results were obtained for Days 3 and 4, whether the animals had two prior days' exposure to baclofen or naltrexone. Second, the results of Experiment 2 show that chronic exposure across 4 days to either baclofen or naltrexone does not produce any change in ethanol consumption, similar to that seen in Experiment 1 across Days 3 and 4.

The mechanism for the additive effect of naltrexone and baclofen is not clear. One possibility, however, is that this effect emanates from effects on both μ opioid and GABAergic receptors in the VTA. Both of these systems appear to be involved in the reinforcing properties of many drugs with abuse potential, including cocaine (Ramsey et al., 1999), morphine (Devine and Wise, 1994), and nicotine (Corrigal et al., 2000). This is suggested by the evidence showing that ethanol is self-administered into the VTA and that, whether self- or experimenter administered, it increases firing of VTA dopaminergic neurons and produces increases in extracellular DA in the Nacc. The VTA is an area relatively rich in both μ opioid and GABAergic receptors, which appear to coregulate common target neurons within the VTA (Sesack and Pickel, 1995). Many of the μ opioid receptors are either collocated with or are located on intrinsic GABAergic interneurons within the VTA (Johnson and North, 1992; Klitenick et al., 1992; Kalivas et al., 1993).

A role for $GABA_A$ receptors in the VTA is suggested by data showing that $GABA_A$ antagonists, pirotoxin and bicuculline, injected into the anterior VTA reduced ethanol self-administration in ethanol-preferring P rats. (Nowak et al., 1998). Alternatively, it has also been suggested that ethanol consumption is modulated either directly or indirectly by μ opioid receptors in the mesolimbic pathway, including the VTA (Cowen and Morgan, 1999; Herz, 1997). In support of this, the administration of acute ethanol has been shown to significantly decrease the binding of [$^3$H]DAMGO at VTA μ opioid receptors (Mendez et al., 2001). The regulation of VTA μ opioid receptors by ethanol, when combined with the evidence showing that ethanol is self-administered into

the VTA (Rodd-Henricks et al., 2000), increases the firing rate of VTA dopamine neurons (Brodie et al., 1990), while increasing extracellular DA in the Nacc (Yoshimoto et al., 1991) suggests that VTA μ receptors are a critical element in those neural pathways underlying ethanol consumption. These μ receptors are located primarily on $GABA_A$ interneurons (Mansour et al., 1988; Dilts and Kalivas, 1989) and have an inhibitory effect, thereby indirectly disinhibiting DA cell bodies in the VTA and increasing extracellular DA in the Nacc by removing tonic inhibition produced by $GABA_A$ interneurons. This same mechanism is hypothesized as a critical element underlying the reinforcing value of opioids (Xi and Stein, 2002). Naltrexone would be hypothesized to have a similar effect on the reinforcing properties of opioids or ethanol. Namely, it would be predicted to block activity at μ receptor sites, preventing GABA disinhibition of VTA dopamine cell bodies.

While this seems to be the most parsimonious explanation for the additive effects of the combination of baclofen and naltrexone, these drugs could act on other pathways that regulate activity in the mesolimbic pathway. For example, there are GABAergic neurons in the Nacc, and μ receptors are located on these neurons as well (Dilts and Kalivas, 1989). This alternative seems less likely because ethanol administered directly into the Nacc is much less effective in releasing extracellular DA in the Nacc compared with the VTA (Wozniak et al., 1991; Yim et al., 1998). Additionally, there are GABAergic pathways from Nacc to the ventral palladium (VP) and to the VTA that are also involved in the regulation of the mesolimbic pathway.

While the precise mechanism for the additive effect of baclofen and naltrexone seen in this experiment remains unclear, the strategy of using multiple drugs to target different pathways, supporting a biologically based, chronic relapsing disease, is a strategy that may be of value and warrants additional research. One potential advantage is that it may permit the use of pharmacotherapies at lower doses. This might have the advantage of reducing or eliminating aversive side effects produced by higher doses. These side effects often contribute to reduced compliance and higher relapse rates.

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