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A comparison of the effects of 6-β naltrexol and naltrexone on the consumption of ethanol or sucrose using a limited-access procedure in rats

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Abstract

We recently reported that 6-β naltrexol, the major metabolite of naltrexone in humans, reduced ethanol consumption in rats. Two new experiments were designed to compare 6-β naltrexol and naltrexone across three dose levels on an ethanol or sucrose baseline using a limited-access procedure in Wistar rats. The results of Experiment 1 showed that both 6-β naltrexol and naltrexone reduced ethanol consumption across a range of doses. An in vivo assay showed that naltrexone was approximately 25 times more potent than 6-β naltrexol at comparable ED_{50} doses. In addition, there was no indication of systematic development of tolerance to the effect of either drug across the 4 days of drug administration. In Experiment 2, both 6-β naltrexol and naltrexone reduced the consumption of a sucrose solution using a limited-access procedure. The implications of these data for the development of pharmacotherapeutic agents capable of reducing drinking in recovering alcoholics are discussed.

Keywords: Ethanol; Sucrose; Naltrexone; 6-β Naltrexol

1. Introduction

Animal models can efficiently screen medications with potential to improve the human condition. For example, the opiate antagonist naltrexone was first shown to reduce ethanol consumption in animal models (Altshuler et al., 1980; Froehlich et al., 1990; Hubbell et al., 1986; Myers and Critcher, 1982; Reid et al., 1991; Volpicelli et al., 1986). These findings led to subsequent successful clinical trials showing that naltrexone reduces alcohol consumption in alcoholics (O'Malley et al., 1992; Volpicelli et al., 1990, 1992, 1997). Although naltrexone is the first new drug to receive FDA approval for the treatment of alcohol dependence in decades, noncompliance with medications and widely variable metabolism in compliant subjects may limit the effectiveness of naltrexone (McCaul et al., 1997; Volpicelli et al., 1997).

In humans, naltrexone has extensive first-pass metabolism and is reduced at the 6-keto-group to the primary metabolite, 6-β naltrexol. In rats, 6-β naltrexol is found in only trace amounts (Misra et al., 1976) suggesting different pharmacokinetics in rats compared to humans. Interspecies differences in naltrexone metabolism have not been closely examined. Naltrexone is a nonselective opioid antagonist with high affinity for *mu* opioid receptors and lesser affinity for *delta* and *kappa* opioid receptors in receptor binding assays (Davis and Nelson, 1995). In these same assays, 6-β naltrexol has a fivefold lower affinity for *mu* receptors than does naltrexone (Davis and Nelson, 1995). However, 6-β naltrexol has both a higher plasma level and longer half-life than naltrexone in humans (Ferrari et al., 1998). Recent evidence in a study of alcoholics showed a significant negative correlation between high plasma levels of 6-β naltrexol and lower reported number of drinks per month (McCaul et al., 2000). Moreover, higher plasma levels of 6-β naltrexol in heavy drinkers correlated with lower subjective measures of "liking" alcohol (McCaul et al., 2000). Although 6-β naltrexol has a lower affinity for *mu* receptors in vitro than does naltrexone in humans, this difference in re-

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ceptor affinity may be offset by 6-β naltrexol's higher plasma concentrations and longer half-life compared to naltrexone. These differences may yield important information for the use of opioid antagonists in clinical treatment.

Since 6-β naltrexol has never been administered to humans and rats do not metabolize naltrexone to 6-β naltrexol, our laboratory provided the first report in any species that 6-β naltrexol administered systemically reduced ethanol consumption in rats (Rukstalis et al., 2000). That experiment left several questions unanswered. The current experiments were designed to examine the dose-response effect of 6-β naltrexol compared to naltrexone on oral self-administration of an ethanol solution in a limited access procedure and to examine the effect of these two drugs on the consumption of a sucrose solution using a similar limited-access procedure to determine if 6-β naltrexol's effect is selective for ethanol.

2. Experiment 1

While it has been demonstrated that both naltrexone and 6-β naltrexol reduce ethanol consumption in rats, there has been no direct comparison of the dose-effect of these drugs on an ethanol baseline. This experiment was designed to compare the effects of naltrexone and 6-β naltrexol on a limited-access ethanol baseline within the same animals. In addition, because our initial experiment examined the effect of a single injection of 6-β naltrexol, this experiment was designed to examine the effect of a more chronic regimen. Rats provide a unique opportunity to examine the effects of these two drugs because 6-β naltrexol is not a metabolite of naltrexone and is found in very small amounts in rat brains but not plasma (Misra et al., 1976). This allows for a direct comparison of the two drugs in a species without the potential confound that is produced by the metabolism of naltrexone in humans.

2.1. Methods

2.1.1. Subjects

Fifty male Wistar rats were purchased from Ace Animals, Boyertown, PA 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 h/12 h reverse light/dark cycle with lights out from 0730 to 1930 h. Animals were provided with ad lib food and water for the entire experiment. Only the 24 highest consuming rats were chosen because they more closely approximated the clinical population of alcohol abusers. These rats drank an average 0.898 g/kg/h ethanol during baseline in the limited-access procedure (range 0.66–1.52 g/kg/h, S.E.M. ± 0.056 g/kg/h). Blood alcohol levels (BAL) were not determined for these animals because the stress of the tail vein procedure disrupts baseline drinking. A comparison of the amount of ethanol consumed by these animals to a historical database of BALs in animals run in the same limited-access procedure in our laboratory suggests that all animals were drinking pharmacologically meaningful amounts of ethanol (i.e., >40 mg/dl). 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.

2.1.2. Procedure

Rats were run in a 1-h limited-access procedure as previously described (Stromberg et al., 1998b). Once ethanol consumption stabilized across the limited-access period (defined as no change in consumption >20% across five consecutive days and requiring 25 days to achieve), the rats were matched for consumption and randomly assigned to one of three groups, a low dose group ($n = 8$), a mid dose group ($n = 8$), and a high dose group ($n = 8$). Animals in each of these groups were given exposure to both 6-β naltrexol and naltrexone counterbalanced for order (e.g., rats in the low dose group were exposed to both the low dose of 6-β naltrexol and the low dose of naltrexone with half of the rats receiving 6-β naltrexol first and the other half receiving naltrexone first.). Animals were next injected with saline 30 min before the limited-access session and for the next 4 days, animals were injected with 6-β naltrexol (15, 25, and 50 mg/kg) or naltrexone (0.1, 1, or 10 mg/kg) 30 min before the limited-access period. Following drug administration, the animals were returned to baseline. A minimum of 7 days was allowed between the test of each dose to allow for drug washout.

2.1.3. Drug

6-β Naltrexol was provided by NIDA. It was dissolved in saline and injected intraperitoneally in doses of 15, 25, and 50 mg/kg. Naltrexone was purchased from Sigma, St. Louis, MO. It was dissolved in saline and injected intraperitoneally in doses of 0.1, 1, and 10 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. These doses were determined based on prior work done in this laboratory using the same animal model. Naltrexone at the doses used in this experiment produced a reduction of ethanol consumption ranging between 40% for the low dose to 80% for the high dose (Stromberg et al., 1998a). The low and medium doses of 6-β naltrexol were chosen based on our initial experiment (Rukstalis et al., 2000), while the high dose was selected based on the fivefold binding difference reported in affinity for the drugs at the *mu* receptor (Davis and Nelson, 1995). Tap water and 95% ethanol were mixed to yield a 6% (v/v) ethanol solution.

2.1.4. Statistical analysis

A repeated-measures ANOVA with two between-subject factors, drug and dose, repeated across three within-subject

treatments, was used to determine if there was an effect for either drug or dose of that drug on ethanol consumption compared to predrug saline or postdrug saline treatment. Drug had two levels, naltrexone and 6-β naltrexol, and dose had three levels, low, medium, and high. Within-subject treatment was repeated across the three distinct treatment periods, predrug saline, the mean of the four drug days collapsed, and the mean of the three postdrug baseline days collapsed. Simple effects tests were used to determine if there were any significant differences in ethanol consumption following predrug saline or each dose of either naltrexone or 6-β naltrexol. Tukey post hoc tests were then used to determine if there were significant differences between the three levels of dose for each drug. While order of drug presentation was counterbalanced across animals, a repeated-measures ANOVA for order of drug presentation, first or second, repeated across the three treatment conditions (predrug saline, drug, and postdrug baseline), was performed to determine if there was a significant effect for order of drug presentation. To determine if there was any evidence for the development of tolerance to either drug presentation, a repeated-measures ANOVA with two between-subject factors, drug and dose, repeated across the within-subject factor of the four drug days, was conducted. Simple effects tests were then performed for each dose of each drug and, if appropriate, Tukey post hoc tests were performed to determine if individual drug days differed from each other. For Experiment 2, a repeated-measures ANOVA of sucrose consumption following drug with two levels, naltrexone and 6-β naltrexol, repeated across two treatment periods, saline and drug, was conducted. Subsequently, pairwise comparisons were performed to determine if sucrose consumption following each drug was significantly different than sucrose consumption following predrug saline.

2.2. Results

Both naltrexone and 6-β naltrexol significantly reduced ethanol consumption when compared to drinking following saline control injections. Fig. 1 shows ethanol consumption following saline injections, the mean of the 4 days of drug injections collapsed, and the mean of the 3 baseline days following injections collapsed. A repeated-measures ANOVA (drug with two levels, 6-β naltrexol and naltrexone, and dose with three levels, low, medium, and high, repeated across three treatment periods) of these data revealed a significant effect for treatment [$F(2,84) = 160.599$, $P < .001$], a significant Treatment × Dose interaction [$F(4,84) = 4.871$, $P = .001$], and a significant Treatment × Drug interaction [$F(2,84) = 4.231$, $P = .018$]. Subsequent simple effects tests revealed that ethanol consumption following each dose of 6-β naltrexol and naltrexone differed significantly from that same consumption following saline injections. Subsequent Tukey post hoc tests revealed that ethanol consumption following naltrexone 1.0 mg/kg differed significantly from ethanol consumption following naltrexone 10.0 mg/kg. There were no significant differences between the means for ethanol consumption following the three 6-β naltrexol doses. Finally, a repeated-measures ANOVA (order of drug presentation repeated across three treatment periods) revealed no significant effect for order of drug presentation.

Fig. 2 shows ethanol consumption following individual 6-β naltrexol (Panel A) and naltrexone (Panel B) injections. A repeated-measures ANOVA of these data (drug, naltrexone, and 6-β naltrexol, by dose, low, medium, and high, repeated across the four drug treatment days) yielded a significant effect for dose [$F(2,42) = 4.212$, $P = .022$] and a significant effect for treatment days [$F(3,126) = 10.845$, $P < .001$]. Subsequent one-way repeated-measures ANOVAs for each drug, at each dose, across the four drug treatment days yielded a

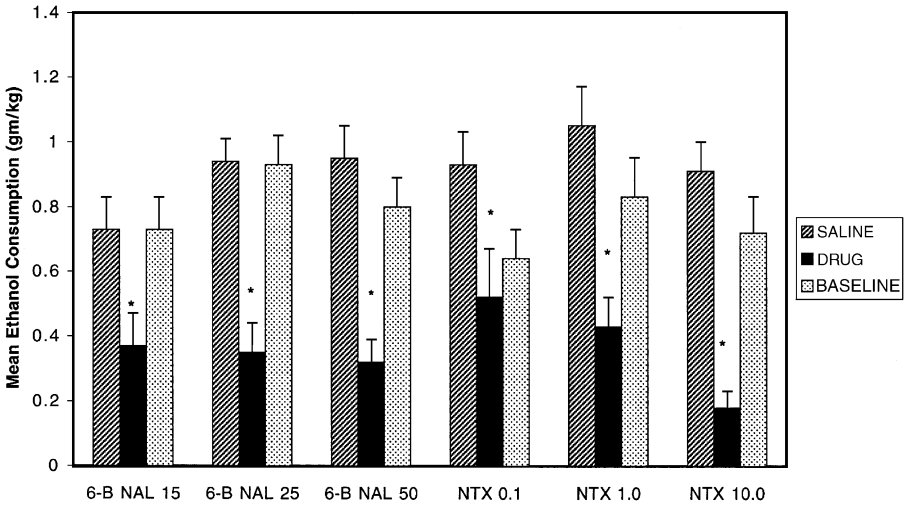

Fig. 1. The effect of 6-β naltrexol (15, 25, and 50 mg/kg) and naltrexone (0.1, 1.0, and 10.0 mg/kg) on ethanol consumption (±S.E.M.) following predrug saline, or drug injections (mean of 4 days collapsed), and postdrug baseline. The asterisks indicate significant differences < .05.

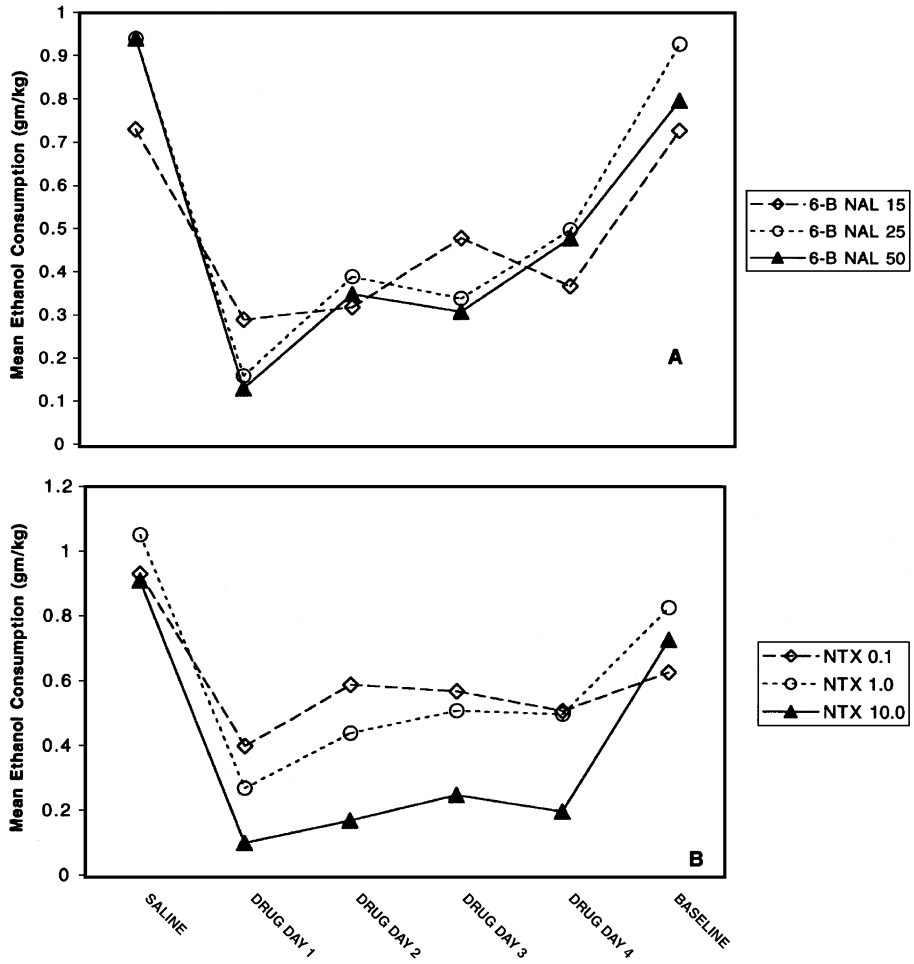

Fig. 2. The effect of 6-β naltrexol (15, 25, and 50 mg/kg) and naltrexone (0.1, 1.0, and 10.0 mg/kg) on ethanol consumption following predrug saline, or individual drug injection days, and postdrug baseline.

significant effect for 6-β naltrexol, 25 mg/kg [$F(3,21) = 7.560$, $P = .001$] and 50 mg/kg [$F(3,21) = 5.548$, $P = .026$] and for naltrexone, 1 mg/kg [$F(3,21) = 3.387$, $P = .037$]. Tukey post hoc tests of these data revealed that ethanol consumption following injection of 6-β naltrexol, 25 mg/kg on Day 1, differed significantly from ethanol consumption on Injection Days 2 and 4 with no other differences. A similar test for 6-β naltrexol 50 mg/kg revealed that ethanol consumption on Injection Day 1 differed significantly from consumption on Injection Day 4 with no other differences. Finally, a Tukey post hoc test of ethanol consumption following naltrexone 1.0 mg/kg revealed that consumption on Injection Day 1 was significantly different from that consumption on Injection Days 3 and 4.

In this experiment, rats drank limited quantities of water (<1.5 ml following predrug saline injections). The general trend was for minor increases in water consumption following all drug administrations with the exception of naltrexone 3.0 and 10.0 mg/kg. None of these changes in water consumption approached statistical significance or produced a meaningful change in ethanol preference measures.

3. Experiment 2

While naltrexone has proven to be an effective pharmacotherapeutic adjunct to psychosocial treatment for alcoholics (O'Malley et al., 1992; Volpicelli et al., 1990, 1992, 1997), preclinical research has demonstrated that it can attenuate other appetitive behavior. For example, systemic naltrexone reduced the consumption of sucrose in rats (Beczkowska et al., 1992) and nonhuman primates (Williams et al., 1998), while administration of naltrexone directly into the nucleus accumbens also reduced sucrose consumption in the rat (Kelley et al., 1996). The goal of this experiment was to compare the effect of a single dose of 6-β naltrexol to naltrexone on the consumption of a sucrose solution using a limited-access procedure.

3.1. Methods

3.1.1. Subjects

Twelve male Wistar rats were purchased from Ace Animals and arrived at the laboratory weighing between

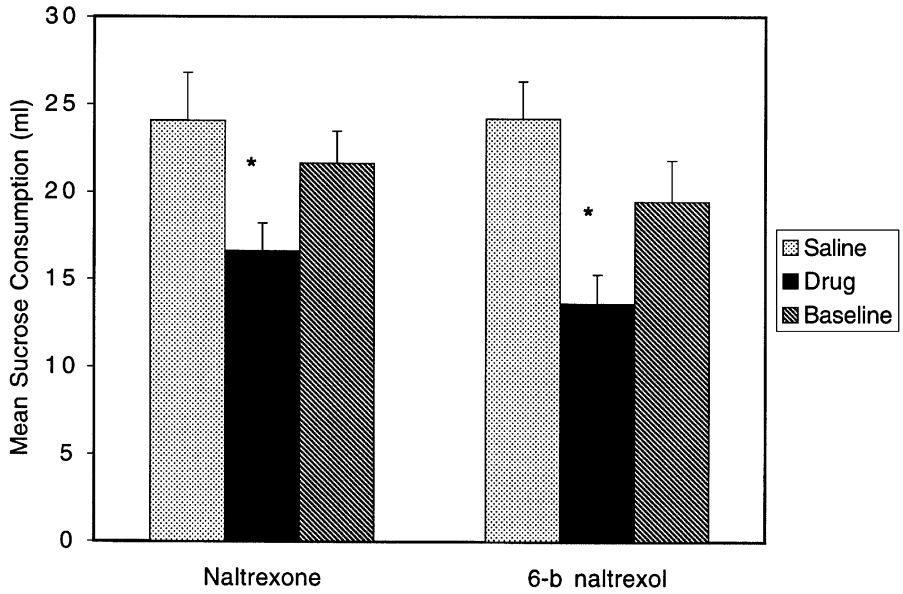

Fig. 3. The effect of 6-β naltrexol, 25 mg/kg, and naltrexone, 1.0 mg/kg, on the consumption of a sucrose solution (10% w/v) (±S.E.M.). The asterisks indicate significant differences $<.05$.

225 and 249 g. The rats were housed in individual acrylic cages in a temperature-controlled (22 °C) animal colony on a 12 h/12 h reverse light/dark cycle with lights out from 0730 to 1930 h. 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 and promulgated by the National Institutes of Health.

3.1.2. Procedure

Rats were first exposed to continuous access to two bottles, one containing tap water and the second a 10% sucrose solution (w/v) until consumption stabilized (see Experiment 1 for description of stability criteria). Both the bottles and the rats were weighed once per day to the nearest 0.1 g between 1100 and 1200 h. Rats were then maintained with ad lib access to food and water and the sucrose solution was presented for 1 h each day. After 9 days of limited access, the rats were matched for consumption and randomly assigned to a 6-β naltrexol ($n=6$) or naltrexone ($n=6$) group. The following day, rats in both groups were injected with saline 30 min before limited access. On the next day, rats in the 6-β naltrexol group were injected with 6-β naltrexol, 25 mg/kg, and rats in the naltrexone group were injected with naltrexone, 1.0 mg/kg 30 min before limited access. On the final 2 days, rats were returned to the limited access baseline.

3.2. Results

Both 6-β naltrexol and naltrexone significantly reduced the consumption of a 10% sucrose solution when compared to sucrose consumption following saline injections. Fig. 3 shows consumption of the sucrose solution following saline injections, drug injections, and a return to baseline. A repeated-measures ANOVA (Treatment × Drug) yielded a significant effect for treatment [$F(1,10)=487.802$, $P<.001$]. Subsequent pairwise comparisons of sucrose consumption following 6-β naltrexol 25 mg/kg and saline [$t(5)=6.844$, $P=.001$] and naltrexone 1.0 mg/kg and saline [$t(5)=4.74$, $P=.005$] were significant.

4. Discussion

The results of the above experiments demonstrate that 6-β naltrexol reduces both ethanol and sucrose consumption like naltrexone. In humans and some experimental animals, 6-β naltrexol has been shown as the major metabolite of naltrexone (Cone and Gorodetzky, 1976; Cone et al., 1974; Misra et al., 1976; Misra, 1981; Verebey et al., 1976; Wall et al., 1981). In rats, only trace amounts of 6-β naltrexol have been detected following the administration of naltrexone (Misra, 1981; Misra et al., 1976). The design of Experiment 1 reported here examined the effects of both drugs at low, medium, and high doses on the consumption of an ethanol solution in the same animals. Because the rat does not metabolize naltrexone to produce 6-β naltrexol, this design has the advantage of being able to compare the effect of these drugs on the same baseline without the potential for confounding the results with drug pharmacokinetics. In addition, evaluating both drugs in the same animal has the advantage of reducing variability arising from a between-subject design.

One goal of these experiments was to compare the effect of both drugs across a range of doses on ethanol consumption. Both naltrexone and 6-β naltrexol share a comparable

affinity for opioid receptor subtypes with the highest affinity for *mu* receptors (Davis and Nelson, 1995). There have been only two comparisons of the potency of 6-β naltrexol and naltrexone on behavioral baselines in rodents. Both of these have examined an analgesia baseline, with 6-β naltrexol reported to have 1/26th or 1/56th the potency of naltrexone (Blumberg and Ikeda, 1976; Fujimoto et al., 1975). While no significant effect for dose or Treatment × Dose interaction was found in Experiment 1 reported here, Fig. 4 shows a stepwise function indicating a dose-response effect for each drug. If we use these data to develop an in vivo assay, the ED_{50} (the dose that produces a 50% change in the behavior) for naltrexone can be set at 1.0 mg/kg and the ED_{50} for 6-β naltrexol at 25 mg/kg. This suggests that the clinically effective dose of 6-β naltrexol may be 25 times greater than that of naltrexone. While the low and medium doses of 6-β naltrexol appear comparable to those of naltrexone, the value for the high dose of 6-β naltrexol does not show an effect comparable to that of the high dose of naltrexone. This suggests that a somewhat higher dose of 6-β naltrexol may be required to achieve effects comparable to those of the high dose of naltrexone. In the experiments reported here, the magnitude of difference between the low and high doses of naltrexone was on the order of 100 ×, while the magnitude of difference for 6-β naltrexol was only approximately 3 ×. Alternatively, it is possible that the results for 6-β naltrexol suggest a ceiling effect. This should be examined in the future by expanding the upper limit of the dose range used in the experiments reported here. Taken as a whole, these results suggest that naltrexone is more potent than 6-β naltrexol.

While potency is an important factor in any comparison of drugs, there are a variety of pharmacokinetic and pharmacodynamic factors that contribute to the overall clinical efficacy of a drug in humans. In this case, the widely variable biotransformation of the parent drug, naltrexone, may be an important, yet unrecognized problem (Ferrari et al., 1998; McCaul et al., 2000). Naltrexone undergoes extensive first-pass metabolism with only 1% of the administered dose excreted as free naltrexone (Cone and Gorodetzky, 1976; Cone et al., 1974). Plasma concentrations of 6-β naltrexol have always been reported as higher than that of naltrexone (Ferrari et al., 1998) and the reported plasma half-life for 6-β naltrexol has also consistently been reported as higher than that of naltrexone (Cone and Gorodetzky, 1976; Cone et al., 1974; Ferrari et al., 1998; Meyer et al. 1984; Verebey et al., 1976; Wall et al., 1981). These differences between parent drug and metabolite may contribute to naltrexone's long duration of action (Bullingham et al., 1983).

Further investigations of the biotransformation process have indicated that there is a large variability in the metabolism of naltrexone with as much as a fourfold difference in peak 6-β naltrexol levels between subjects receiving naltrexone (Ferrari et al., 1998; McCaul et al., 1997, 2000; Verebey et al., 1976). To the extent that 6-β naltrexol levels may predict clinical efficacy, control over the amount of drug that enters the body and then reaches the critical receptor sites may prove critical to outcome. If 6-β naltrexol has a more reliable biotransformation profile, it may have a clinical utility to provide more precise control over dose compared to the variability currently experienced with naltrexone. The potential importance of 6-β naltrexol was demonstrated in recent clinical investigations demonstrating a negative relationship between serum levels of 6-β naltrexol and the number of drinks consumed (McCaul

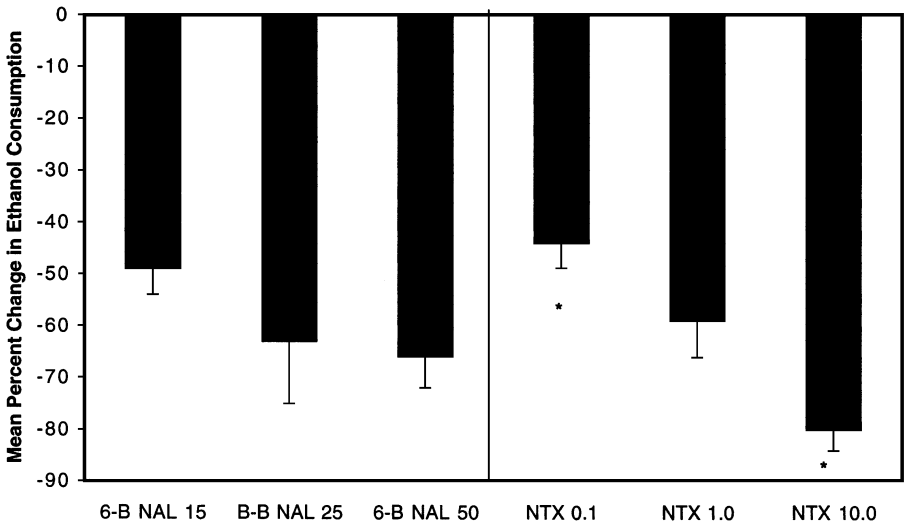

Fig. 4. The percentage change in ethanol consumption (±S.E.M.) following 6-β naltrexol (15, 25, and 50 mg/kg) and naltrexone (0.1, 1.0, and 10.0 mg/kg). Percentage change was determined as follows: ethanol consumption following predrug saline minus mean of ethanol consumption following four drug injections collapsed divided by ethanol consumption following predrug saline. The asterisks represent doses of drug that differ significantly from one another $< .05$.

et al., 2000) and the positive relationship between serum 6-β naltrexol levels and the subjective rating of "liking" a high dose of alcohol in heavy drinkers (McCaul et al., 1997). Since serum levels of 6-β naltrexol have also been linked to negative side effects of naltrexone in one acute alcohol self-administration study (King et al., 1997), control of dosing may reduce these effects while maintaining clinical efficacy with the attendant benefit of increasing medication compliance. This becomes critical as the effectiveness of naltrexone as a pharmacotherapeutic adjunct to psychosocial treatment of alcoholism has recently been identified as related to compliance (Volpicelli et al., 1997).

A second goal of these experiments was to compare the effects of these two drugs across a more chronic exposure to determine if there was evidence for the development of tolerance. While the data shown in Fig. 2 suggest that there was a trend for the rats to increase ethanol consumption across days of drug administration, the differences revealed by the analysis of the drug effects on ethanol consumption were widely variable and inconsistent with a pattern suggesting the systematic development of tolerance to either drug. Those differences that did emerge may have been due to initial dramatic changes in ethanol consumption following the first drug injection as opposed to systematic changes in consumption across the following 3 days. For example, ethanol consumption following 6-β naltrexol 25 mg/kg injections was significantly higher on Days 2 and 4 than on Day 1, but not on Day 3, while consumption following 6-β naltrexol 50 mg/kg was significantly higher only on Day 4 when compared to Day 1. Further, ethanol consumption following naltrexone 1.0 mg/kg on Days 3 and 4 was significantly higher than on Day 1, with no differences in either the high- or low-dose conditions. Previous work in this laboratory has shown that tolerance did not develop across either 30 or 60 days of repeated daily administration of naltrexone, 1.0 mg/kg (Stromberg et al., 1998b). These results suggest that tolerance does not develop to repeated daily systemic injections of opioid antagonists. However, there is additional data suggesting that continuous exposure to opioid antagonist, naloxone, using an osmotic minipump produces tolerance through up-regulation of *mu* opioid receptors. This appears to be due to the continuous exposure of opioid receptors to the antagonist because acute administration of naloxone produced no evidence of tolerance in this same series of experiments (Overstreet et al., 1999). Because the affinity of naltrexone for *mu* receptors is dose sensitive, it would be predicted that tolerance related to receptor up-regulation would be greater for naltrexone 10 mg/kg than for naltrexone 1 mg/kg. In addition, 6-β naltrexol has a fivefold lower affinity for *mu* opioid receptors than does naltrexone (Davis and Nelson, 1995), so it should be expected that 6-β naltrexol would produce less receptor up-regulation and subsequent tolerance. However, neither of these patterns appeared in the data of the experiments reported here. When considered in this context, it is suggested that the pattern of data across the 4 days of drug administration was not due to the systematic development of tolerance.

Finally, opioid antagonists have been demonstrated to reduce many appetitive baselines, including sucrose (Beczkowska et al., 1992; Kelley et al., 1996). The results from Experiment 2 demonstrate that 6-β naltrexol reduces consumption of a sucrose solution as well as consumption of an ethanol solution. This reduction in baseline sucrose consumption was comparable to that of naltrexone and suggests that the action of both 6-β naltrexol and the parent drug, naltrexone, is consistent across appetitive baselines.

In summary, the present data extend our initial report (Rukstalis et al., 2000) that 6-β naltrexol reduces ethanol consumption in the rat. In addition, it provides a dose-effect comparison of 6-β naltrexol to naltrexone on an ethanol baseline demonstrating a lower potency for 6-β naltrexol, compared to naltrexone that varies widely across the range of doses. Across the length of this experiment, there was no systematic evidence for the development of tolerance of either drug's ability to attenuate ethanol consumption. The effects of 6-β naltrexol were not limited to an ethanol baseline but extended to sucrose as well. These data are consistent with naltrexone's effect on both these baselines. Future experiments could explore the oral bioavailability of 6-β naltrexol and the duration of action of 6-β naltrexol compared to naltrexone. These data may be important in developing new medications or by improving clinical efficacy with the use of the parent drug naltrexone.

Acknowledgments

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