Beta-Adrenergic Antagonists Attenuate Somatic and Aversive Signs of Opiate Withdrawal

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The current studies were designed to evaluate the effectiveness of β-adrenergic antagonists on opiate withdrawal symptoms utilizing a variety of paradigms. Male Sprague-Dawley rats were made moderately dependent on morphine with daily incremental injections. Both the nonselective β-antagonist propranolol and the selective β_1-antagonist atenolol, in the dose range of 5 to 20 mg/kg, were found to significantly reduce many of the somatic responses to either naloxone-precipitated or abstinence-induced withdrawal from morphine. In addition, propranolol (10 mg/kg) significantly reduced a withdrawal-induced conditioned place aversion, while atenolol was effective only at the highest dose tested (20 mg/kg). These data indicate that β-adrenergic antagonists might be effective in the treatment of opiate addictions. ***[Neuropsychopharmacology 9:303–311, 1993]***

KEY WORDS: *Morphine; Opiate dependence; Opiate withdrawal syndrome; Beta-adrenergic antagonists; Propranolol; Atenolol*

Withdrawal from chronic opiate use in humans has been described as a mixture of anxiety and dysphoria that is accompanied by a variety of physical symptoms such as chills, nausea, and diarrhea (Jaffe, 1985). The aversiveness of these symptoms, and their precipitation by drug-conditioned environmental cues, is speculated to contribute to the high incidence of relapse among former addicts attempting to abstain from opiate use (Childress et al. 1986).

There is considerable evidence indicating that central noradrenergic systems are hyperactive during withdrawal from chronic opiates and may contribute to the opiate withdrawal syndrome. Naloxone-precipitated withdrawal produces a marked increase in the firing of noradrenergic locus ceruleus (LC) neurons (Aghajanian 1978; Akaoka and Aston-Jones 1991) and a corresponding increase in circulating levels of 3-methoxy-4-hydroxyphenethylene glycol, the principle metabolite of norepinephrine (NE) (Korf et al., 1974). Direct correlations have been reported between the time course of the increased activity of LC neurons and the presence of overt somatic symptoms during naloxone-precipitated withdrawal (Rasmussen et al. 1990). Furthermore, the region of the LC has been reported to be one of the most sensitive sites in the brain for producing overt somatic signs of opiate withdrawal following local administration of an opiate antagonist (Maldonado et al. 1992). The α_2-adrenergic agonist clonidine prevents the withdrawal-induced increase in LC activity (Aghajanian 1978), the increase in NE metabolites (Crawley et al., 1979), and a majority of the withdrawal symptoms (Tseng et al. 1975; Meyer and Sparber 1976), even when microinjected into the LC (Taylor et al. 1988).

If NE release is important for the manifestation of some or all of the opiate withdrawal syndrome, then blockade of postsynaptic α_1- and/or β-adrenergic receptors should reduce the severity of some or all of the withdrawal symptoms. In the few studies that have

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tested this hypothesis, it was reported that α_1 antagonists reduce some signs of withdrawal (Cicero et al. 1974; Valeri et al. 1989), but it was reported in these studies and others that the β-antagonist, propranolol, had no effect on the somatic signs of precipitated opiate withdrawal (Jhamandas et al. 1973; Cicero et al. 1974; Chipkin et al. 1975). Recently, we found that β-adrenergic antagonists were effective in reducing abstinence-induced anxiety-like behaviors in both chronic morphine- and cocaine-treated rats (Harris and Aston-Jones 1993). These data indicated that β-adrenergic antagonists could be useful in the treatment of addiction. Furthermore, previous reports have noted the effectiveness of β-antagonists in treating alcohol withdrawal symptoms (Carlsson, 1976). In the human literature, there have been conflicting reports on the effectiveness of propranolol in treating heroin addicts. Two reports have indicated that propranolol was effective in reducing withdrawal symptoms (Roehrick and Gold 1987) and alleviating craving (Grosz 1972), whereas two other reports concluded that the effectiveness of propranolol was too limited to warrant further investigation (Hollister and Prusmack 1974; Resnick et al. 1976).

The purpose of the present experiments was to reevaluate the effectiveness of propranolol in treating opiate withdrawal symptoms using a variety of paradigms. We tested the effectiveness of propranolol on the somatic signs of naloxone-precipitated withdrawal (as in the previous studies) and also on somatic signs of abstinence withdrawal. Furthermore, we have used place-conditioning paradigms to determine if β-adrenergic antagonists are effective in blocking the development of withdrawal-induced place aversions. The β-adrenergic antagonists that were used in this study include the nonselective $\beta_{1/2}$-antagonist, propranolol, as well as the selective β_1-antagonist, atenolol.

METHODS

Subjects

The subjects were 135 male Sprague-Dawley rats weighing between 200 and 250 g, purchased from Taconic Farms (Germantown, NY). Rats were housed in accordance with National Institutes of Health guidelines with food and water available ad lib. A 12-hour light/dark cycle was in effect throughout the experiment.

Drugs

Morphine sulfate was provided by the National Institute on Drug Abuse and was dissolved in saline. Propranolol and atenolol were purchased from Sigma Chemical Company (St. Louis, MO) and were dissolved in distilled water.

Chronic Drug Treatment

Rats receiving chronic morphine treatment were injected intraperitoneally (IP) once daily at 4:00 PM. On Day 1, the dose was 10 mg/kg and the doses were increased incrementally by 10 mg/kg every day until rats received 80 mg/kg, after which they were maintained at 60 mg/kg per day for the duration of the experiment. At the dose level of 60 mg/kg per day, animals maintained their weight or gained small amounts of weight. At higher doses (80 to 90 mg/kg/day) animals appeared to be sick and lost considerable amounts of weight within a week.

Measurement of Somatic Responses to Withdrawal

Rats were tested in the morning, approximately 16 hours after the previous morphine injection, in the rat colony room. Each rat was placed alone in a 24- × 45- × 21-cm Plexiglas chamber, the floor of which was covered with commercially available corn cob bedding material. No more than two rats were scored at the same time. Fifteen minutes prior to a 0.5 mg/kg IP dose of naloxone, rats were pretreated with saline (n = 10), propranolol (2 mg/kg [n = 6]; 5 mg/kg [n = 8]; 10 mg/kg [n = 8]; 15 mg/kg [n = 7]; 20 mg/kg [n = 7], IP) or atenolol (5 mg/kg [n = 6]; 10 mg/kg [n = 9]; 15 mg/kg [n = 7]; 20 mg/kg [n = 6], IP). Additional experiments were performed to determine if the amount of time after the last morphine injection influenced the findings. In these experiments, rats (n = 17) were given morphine (30 mg/kg) on the morning of the test day and given naloxone 2 hours later. In these experiments, saline, propranolol, or atenolol (10 mg/kg; n = 6 for each group) was injected 15 minutes prior to naloxone.

The behavioral rating scale employed was similar to that reported by Blasig et al. (1973). Instances of the following behaviors were counted for 30 minutes after naloxone administration: wet dog shakes (whole-body shaking), teeth chatter (grinding of teeth, grossly calculated as number of episodes, maximal count of 1 per 30 seconds), writhing (abdominal stretching), eye twitching (rapid closing of the eye lid), diarrhea (number of episodes), and jumping (leaping onto the edge of the chamber). In addition, every 10 minutes animals were scored for the presence or absence of the following behaviors: vocalizing on touch, ptosis (drooping of the eye lids), rhinorrhea, lacrimation, and piloerection. These parameters were distinctive and easily measured so that blind observations were not necessary. Nonetheless, several animals in some of the groups were scored by blind observers (propranolol 5 mg/kg, n = 2; propranolol 10 mg/kg, n = 3; atenolol 10 mg/kg, n = 3; atenolol 15 mg/kg, n = 2; vehicle, n = 2). As the mean scores for animals scored blind were nearly identical to scores for those not scored blind, the data from both

observation methods were pooled to form one score for each particular drug treatment group.

For similar measures during abstinence withdrawal, other rats were placed in the Plexiglas test chamber 1 hour prior to the daily morphine injection (23 hours after the last morphine injection) and scored using the same rating scale that was used to measure precipitated withdrawal signs. Rats were observed for 30 minutes to obtain data on baseline measurements of withdrawal signs. Following this period, rats were injected with saline (n = 10), propranolol (5 mg/kg [n = 8], 10 mg/kg [n = 6], or atenolol (5 mg/kg [n = 6], 10 mg/kg [n = 6], IP). Fifteen minutes after these injections, rats were again scored for the incidence of withdrawal behaviors for 30 minutes.

Measurement of Place Aversion

The place conditioning apparatus was a 70- × 30- × 45-cm box divided equally into two compartments. The first compartment had a smooth clear Plexiglas floor, black spots on the rear wall, and an almond scent. The second compartment had a rough opaque Plexiglas floor, black stripes on the rear wall, and an orange scent. Scents were applied sparingly to walls on opposite ends of the apparatus. A separate group of rats (n = 22) was used in these experiments. All rats were tested in the morning 16 hours to 18 hours after the last morphine injection.

Day 1: Preconditioning Phase. On the first day, each rat was allowed to freely explore both compartments of the box, and the amount of time spent on each side was recorded for 20 minutes. Any rat showing a strong preference for either side (>13 minutes) was removed from the study; only two animals had to be eliminated for this reason.

Days 2 and 3: Conditioning Phase. On day 2, rats were injected with either saline, propranolol (10 mg/kg IP) or atenolol (10 or 20 mg/kg, IP) 15 minutes prior to an injection of either saline or 0.2 mg/kg of naloxone (IP).

The environment to be paired with naloxone was chosen in a quasirandom order so that equal numbers of animals in each group were assigned to be given naloxone in the two different sides. Immediately following the naloxone or saline injection, rats were confined to one side of the box by means of an opaque Plexiglas divider for 20 minutes. On day 3, rats were given the same pretreatment as on day 2 and confined to the opposite compartment following either a saline or naloxone injection. Animals within each group were counterbalanced so that half of the animals in each group received the naloxone injection on day 2 and the other half on Day 3.

Day 4: Test Phase. Rats were given free access to both compartments and the amount of time spent on each side was recorded for 20 minutes.

Data Analysis

Data for somatic measures of precipitated and abstinence withdrawal experiments were analyzed using a one-way analysis of variance (ANOVA) (on dose) for each withdrawal measure. Post-hoc follow-up tests on significant interactions were done using Newman-Keuls' tests. The data from the place-aversion experiment were analyzed using the nonparametric Kruskal-Wallis test. An aversion score was calculated for each subject by subtracting the amount of time spent on the naloxone paired side prior to conditioning (day 1) from the amount of time spent on that side after conditioning (day 4). Post-hoc comparisons were made using the Mann-Whitney U test.

RESULTS

Naloxone-Precipitated Withdrawal

The most prominent somatic signs of precipitated withdrawal were wet dog shakes, teeth chatter, writhing, vocalization on touch, ptosis, eye twitch, and diarrhea. Only a few animals (n = 4) exhibited rhinorrhea or piloerection and none showed jumping or lacrimation. Only the most consistent signs of withdrawal (listed above) were included in the data analysis. Figure 1A and B shows the instances of withdrawal behaviors following pretreatment with propranolol or atenolol, respectively. All doses of each drug significantly reduced all somatic withdrawal measures. Vehicle-treated animals typically became inactive and laid supine on the bottom of the cage following precipitated withdrawal. In contrast, animals treated with β-blockers typically remained active during the entire observation period after naloxone and continued to explore the test cage. Animals given β-blockers in the range of 5 mg/kg to 15 mg/kg were significantly more likely to be given a rating of active ($p < .01$) than were the vehicle-injected animals.

The β-blockers appeared to be less effective at attenuating somatic withdrawal symptoms in animals given naloxone 2 hours as compared to 16 hours after a morphine injection (Fig. 2). These differences reached statistical significance for measures of wet dog shakes, teeth chatter, and writhing for the propranolol-treated group ($p < .01$). However, only wet dog shakes in the 2-hour group were not attenuated compared to vehicle-treated animals. Similarly, in the atenolol-treated groups, there were significantly more wet dog shakes, ptosis, and writhing in the animals subjected to with-

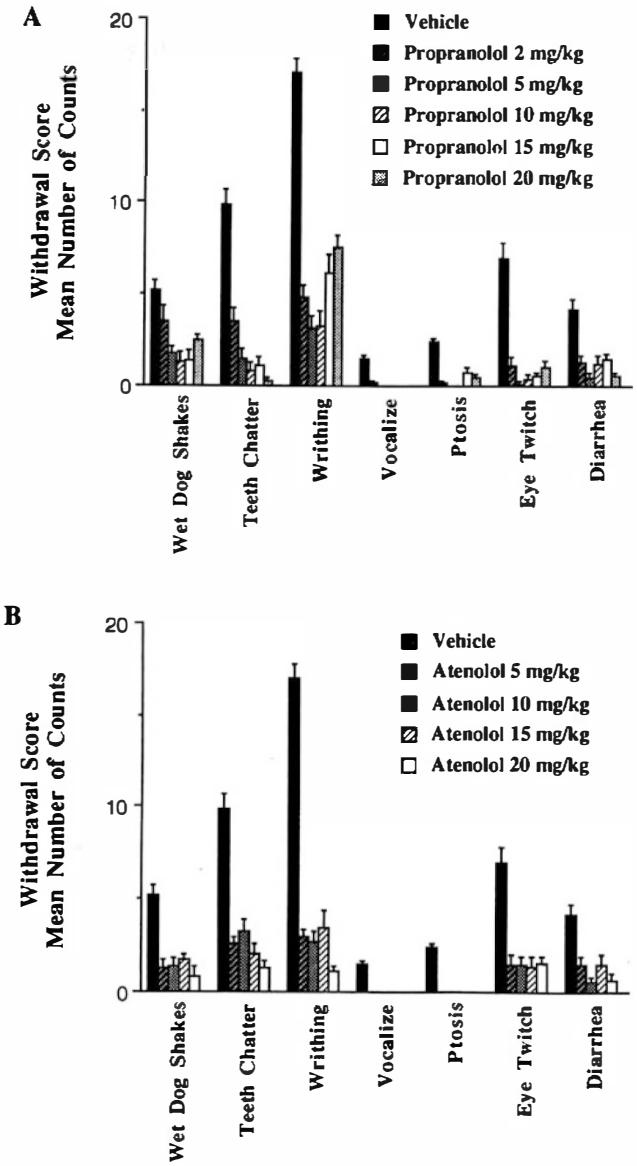

Figure 1. Mean number of counts (± the SEM) for each behavior measured during naloxone-precipitated withdrawal. The response to different doses of propranolol is shown in **A**, and **B** shows the response to atenolol doses. When compared to the vehicle-treated group, the drug-treated groups were significantly different on the following measures: wet dog shakes: propranolol, $p < .05$ for each dose; atenolol, $p < .01$ for each dose; teeth chatter, writhing, vocalization on touch, ptosis, and eye twitch: propranolol and atenolol $p < .001$ at each dose; diarrhea; propranolol and atenolol $p < .01$ at each dose.

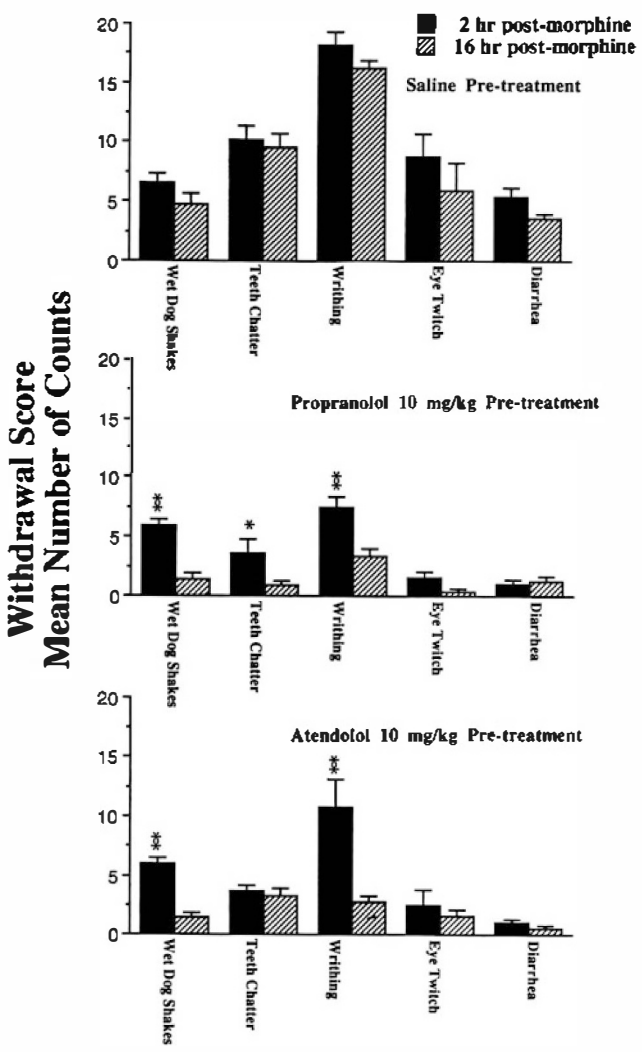

Figure 2. Mean number of counts (± SEM) for each withdrawal behavior measured during naloxone-precipitated withdrawal 2 hours or 16 hours after the previous morphine injection. Propranolol and atenolol (10 mg/kg) were less effective at reducing withdrawal elicited by naloxone given 2 hours compared to 16 hours after the last morphine injection. Significance levels refer to 2-hour versus 16-hour data within each drug group. ** $p < .01$, * $p < .05$.

drawal 2 hours postmorphine compared to 16 hours postmorphine ($p < .01$). Again, however, only wet dog shakes in the 2-hour group were not attenuated by this β-antagonist relative to vehicle-treated animals.

Abstinence Withdrawal

Figure 3 shows the effects of vehicle, propranolol, or atenolol on somatic signs of abstinence withdrawal. The primary somatic symptoms elicited by abstinence in all of the animals prior to treatment were wet dog shakes, teeth chatter, writhing, and eye twitching. There was no significant difference between any of the groups in the number of abstinence signs measured prior to treatment with vehicle or the β-blockers. There was no significant difference in the number of any signs measured pre- versus postinjection with vehicle treatment. For both doses of propranolol, however, there was a significant decrease in the number of abstinence signs seen following the injection, relative to levels seen preinjection or after vehicle injections.

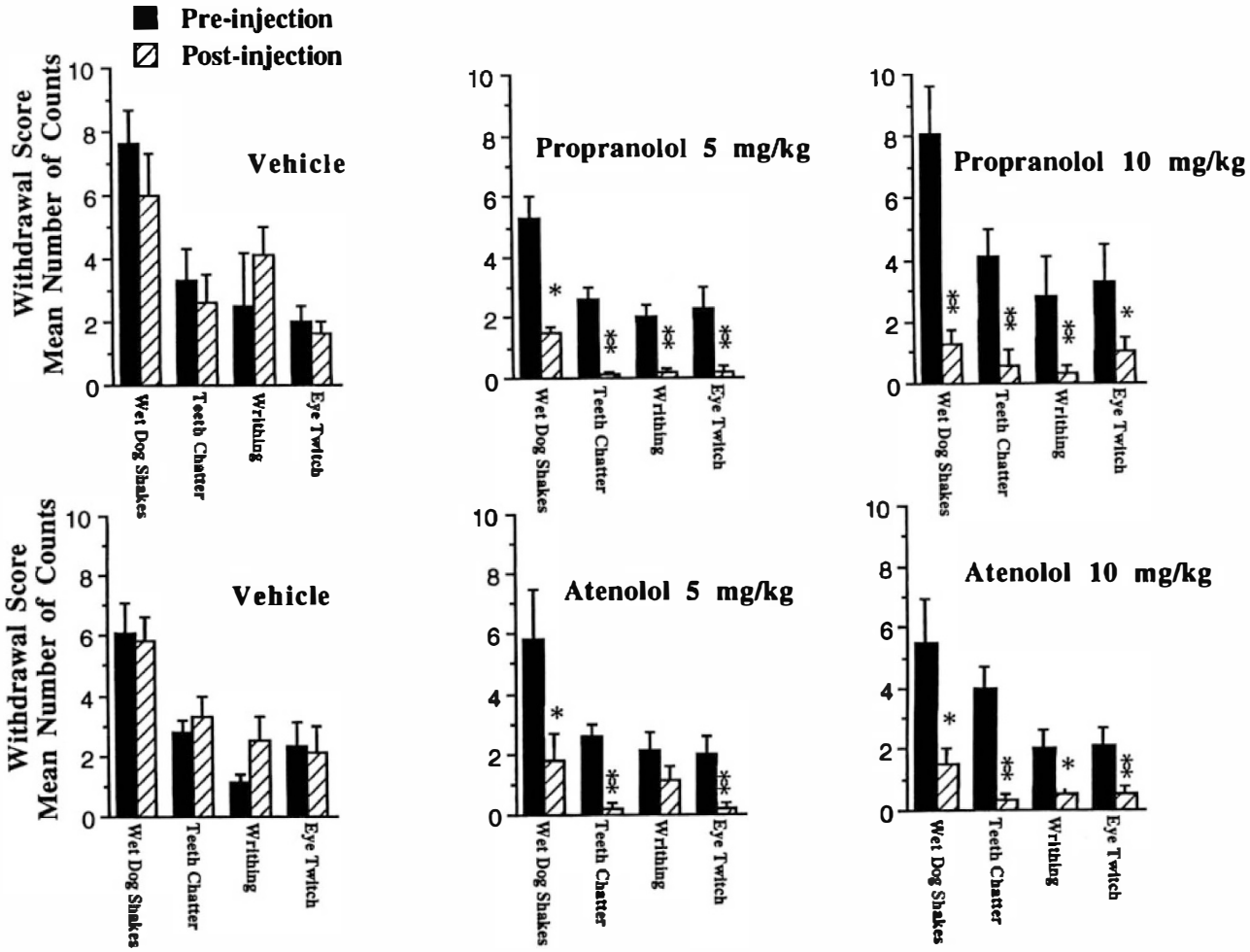

Figure 3. Mean number of counts (± SEM) for each withdrawal behavior measured during abstinence-induced withdrawal before (pre) and after (post) injections of vehicle, propranolol, or atenolol. There was a significant decrease in withdrawal signs following propranolol treatment at both 5 mg/kg and 10 mg/kg doses as compared to pretreatment values: wet dog shakes, teeth chatter, $p < .01$; writhing, eye twitch, $p < .05$. This was also true for atenolol treatment at 5 mg/kg and 10 mg/kg doses: wet dog shakes, $p < .05$, teeth chatter and eye twitchs: $p < .01$, atenolol 10 mg/kg: writhing, $p < .05$. When compared to vehicle-treated animals, propranolol and atenolol animals also showed a significant decrease in withdrawal signs postinjection (propranolol 5 mg/kg and 10 mg/kg: wet dog shakes, writhing, $p < .01$; teeth chatter, $p < .05$; propranolol 5 mg/kg: eye twitch, $p < .05$; atenolol 5 mg/kg and 10 mg/kg: wet dog shakes and teeth chatter, $p < .01$, eye twitch, $p < .05$).

Similar results were seen with both doses of atenolol. There was a significant decrease in abstinence withdrawal signs following atenolol treatment relative to preinjection measures and atenolol-treated animals exhibited significantly fewer signs than vehicle-treated animals posttreatment.

Place Aversion

There was no significant preference for either compartment before naloxone treatment (day 1), and all rats spent approximately equal amounts of time on both sides. After conditioning, the rats treated with saline on day 2 or 3 showed a strong aversion to the side paired with naloxone (Fig. 4), spending an average of only 2 minutes on that side. Administration of propranolol (10 mg/kg) significantly reduced this aversion ($Z = -2.88$, $p < .004$, Fig. 4), whereas the same concentration of atenolol was not significantly effective. A higher concentration of atenolol (20 mg/kg) significantly reduced the withdrawal aversion ($Z = -2.88$, $p < .004$; Fig. 4).

In one group of chronically morphine treated animals ($n = 4$), propranolol (10 mg/kg) was tested on its own in the place-conditioning apparatus. Testing was done in the morning before animals exhibited abstinence withdrawal. These experiments were conducted in a similar manner to that used for place-aversion conditioning with the 4-day protocol. On days

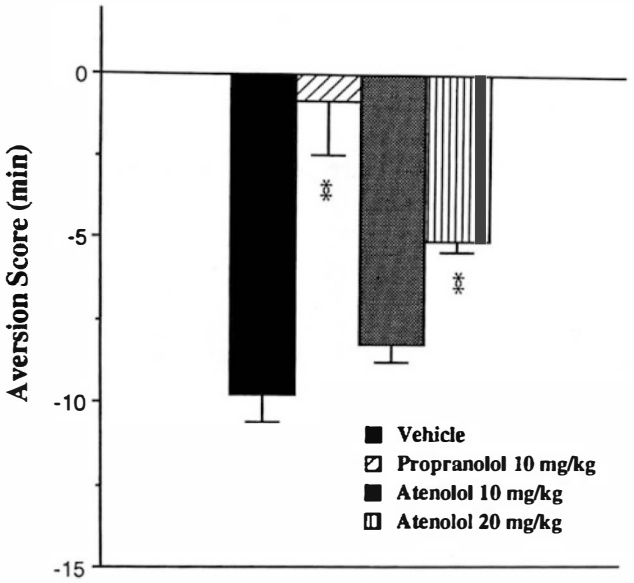

Figure 4. Aversion scores, calculated by subtracting the amount of time spent in the naloxone-paired environment postconditioning from the amount of time spent in the same environment prior to conditioning. Treatments refer to the injections given to each group 15 minutes prior to conditioning on both days 2 and 3. Significance levels refer to the vehicle-treated group, ** $p < .01$.

2 and 3, an injection of propranolol was paired with one side of the apparatus while a vehicle injection was paired with the other side. Propranolol was found to have no significant valence of its own. The mean change in the amount of time spent on the propranolol side was 0.30 ± 0.60 minutes after conditioning.

DISCUSSION

These data indicate that β-adrenergic antagonists can be effective in alleviating many of the somatic signs of both naloxone-precipitated and abstinence-induced opiate withdrawal. Both propranolol and atenolol significantly reduced all of the somatic signs of withdrawal measured in the current experiment. Furthermore, propranolol was also found to be effective in blocking the development of a conditioned place aversion to an environment associated with naloxone administration in morphine-dependent animals.

Both β-blockers appeared to be equally effective in attenuating the somatic symptoms of withdrawal. Because atenolol acts preferentially at peripheral β_1-receptors and enters the brain in only limited amounts (Gilman et al. 1985; Agon et al. 1991), this may indicate that peripheral β_1-receptors play a primary role in the initiation of some withdrawal symptoms. It has been shown that central injections of methylnaloxonium can elicit powerful somatic withdrawal reactions, thereby indicating a central site of origin for many withdrawal symptoms (Maldonado et al. 1992). However, it is possible that peripheral β-adrenergic receptors become involved in the somatic withdrawal reaction following activation by a central sympathetic cascade. For propranolol, the most effective doses for alleviating somatic signs of opiate withdrawal were in the range of 5 mg/kg to 10 mg/kg. Lower doses and higher doses had reduced effectiveness. In contrast, atenolol was equally effective at each dose tested from 5 mg/kg to 20 mg/kg. It could be that at the higher doses, propranolol has other effects that interfere with its ability to decrease withdrawal symptoms. For example, unlike atenolol, propranolol binds to serotonin receptors and can act as a local anesthetic (Gilman et al. 1985; Middlemiss et al. 1977).

When animals were given naloxone 2 hours after a morphine injection, both propranolol and atenolol were less effective in reducing withdrawal symptoms than in animals given naloxone 16- hours after the last morphine injection. A major difference between 2- and 16-hour postmorphine treatment is the concentration of circulating morphine, which is presumably much lower in the latter. The severity of withdrawal might be linked to the number of activated opiate receptors that are subsequently blocked by naloxone. Therefore, the β-blockers may have been less efficacious 2 hours after morphine because the withdrawal reaction was more severe. However, there was no significant increase in withdrawal behaviors in animals withdrawn 2 hours versus 16 hours after morphine when they were not given a β-blocker. The failure to find increased withdrawal behaviors in the vehicle-treated 2-hour group may reflect a ceiling effect that prevented withdrawal behaviors from increasing in measurable intensity beyond that seen in the 16-hour group.

The findings in the place-aversion study are consistent with those of a previous study that showed that the pairing of a distinctive environment with naloxone in opioid-dependent rats can produce an aversion to that environment (Hand et al. 1988). In the current study, β-adrenergic antagonists were found to be effective in reducing this aversion. One possible explanation for these results is that propranolol itself is aversive and by pairing both sides of the apparatus with propranolol, both sides of the apparatus became equally aversive. However, in a separate test, it was found that propranolol had no significant valence on its own, thereby indicating that propranolol could not have influenced the results by being either aversive or rewarding. A second possibility could be that the β-blockers caused the animals to forget what had happened to them during the conditioning phase. This possibility is also not likely because similar doses used in a previous study (Harris and Aston-Jones 1993) did not cause animals to forget an aversive electric shock.

A lower dose of naloxone was used in these experiments for precipitating withdrawal (compared to the somatic withdrawal studies) to produce mild somatic symptoms of withdrawal while maintaining place aversions. Previous research has indicated that the brain areas most sensitive for producing aversion are different from those producing somatic responses to withdrawal. In a recent review by Koob et al. (1992), it was stated that the regions of the LC and periaqueductal gray were the most sensitive sites for producing somatic symptoms of withdrawal, whereas the nucleus accumbens was the most sensitive site for producing withdrawal aversions. It is possible that interactions between the LC and the nucleus accumbens influence withdrawal aversions. For example, it has been reported that naloxone-precipitated withdrawal decreases extracellular dopamine levels in the accumbens and that this effect can be blocked by pretreatment with the adrenergic agonist, clonidine (Pathos et al. 1991). It has been speculated that the decreased dopamine levels in the accumbens could be the neural substrate responsible for the withdrawal-induced place aversions (Acquas et al. 1991; Pathos et al. 1991; Rossetti et al. 1992). Furthermore, it is thought that clonidine alleviates some withdrawal signs by decreasing central noradrenergic output (Taylor et al. 1988).

In the current place-conditioning experiments, propranolol was so effective in preventing the development of place aversion that animals spent equal amounts of time in each environment, regardless of any associations with naloxone. Atenolol was much less effective than propranolol in reducing place aversions, producing significant effects only at the highest dose. This difference may reflect atenolol's much more limited access to the central nervous system after systemic administration (Agon et al. 1991) and may indicate that blockade of central β-receptors is necessary to block place-aversion development. In a previous study, it was found that high doses of methylnaloxonium (10 mg/kg) were required to produce place aversion when given systemically, but only small concentrations (50 ng) were required to produce the same effect when administered centrally (Hand et al. 1988). The present data are consistent with these results and may also indicate that aversive aspects of opiate withdrawal are mediated at central locations. Although there are a substantial number of β-adrenergic receptors in the accumbens, β-receptors are also located throughout much of the central nervous system (Rainbow et al. 1984). Additional experiments directly comparing central with peripheral β-antagonist administration would be necessary to confirm exactly where propranolol was working to alleviate withdrawal aversion.

The finding in the current study that the β-antagonists were effective in reducing naloxone-precipitated opiate withdrawal signs is contrary to what has been reported previously (Jhamandas et al. 1973; Cicero et al. 1974; Chipkin et al. 1975). This discrepancy may reflect the different methods used to induce morphine dependence. In both the Cicero et al. (1974) and Chipkin et al. (1975) studies, morphine pellets were used to allow for continuous morphine treatment. In the studies by Jhamandas et al. (1973) and Chipkin et al. (1975) animals were given multiple daily injections of morphine in the dose range of 200 mg/kg to 300 mg/kg per day. In the current study, animals were given morphine injections once daily and maintained at a moderate dose of 60 mg/kg per day. This dosing regimen maintained healthy animals throughout the experimental phase. In addition, although naloxone precipitated a substantial withdrawal syndrome in these animals, indicating that they were dependent, it did not consistently elicit certain characteristic signs such as rhinorrhea, lacrimation, and jumping that have been reported to occur with more intensive treatment regimens. Data from the current study, when viewed with the data from these previous studies, indicate that β-blockers may be most effective in reducing opiate withdrawal in moderately dependent subjects. Additional studies would be required, comparing the ability of propranolol to alleviate withdrawal signs in animals with different levels of morphine dependence, to determine if this hypothesis is true. This hypothesis is, however, consistent with previous clinical studies. In the two papers that found propranolol to be effective in the mitigation of withdrawal in human opiate addicts (Grosz 1972; Roehrick and Gold 1987), the patients were already in various stages of detoxification, whereas in the other studies with negative results, the patients were just beginning detoxification. Differences in the level of dependence in the human subjects between these studies could explain the discrepancies in their findings.

The current study also found that propranolol was effective in reducing signs of abstinence withdrawal, a milder form of withdrawal than that produced by naloxone. None of the previous studies examined abstinence withdrawal, and, therefore, it is unknown if propranolol would be effective in alleviating abstinence signs with the more intensive morphine treatment regimens.

The present results indicate that β-blockers may be useful in treating patients who have mild opiate addictions or who are trying to reduce or eliminate maintenance doses of methadone. Currently, clonidine is the only nonopiate pharmaceutical treatment that is generally effective in such patients. Clonidine, however, produces drowsiness, restlessness, and hypotension (Charney et al. 1981). In the current study, propranolol was effective at a low dose range, and, therefore, the high doses that have been tried in patients in the past may not be necessary. Lower doses of propranolol would not produce drowsiness, restless-

ness, or severe hypotension and may be preferred over clonidine. Alternatively, propranolol may be useful as an adjunct to clonidine therapy, as was reported in an earlier paper (Roehrick and Gold 1987).

Previously, we have shown propranolol and atenolol to be very effective in alleviating anxiety-like behaviors in animals withdrawing from opiates (Harris and Aston-Jones 1993). Former addicts often report anxiety and conditioned withdrawal reactions when they return to a drug-associated environment (Childress et al. 1986). These reactions may precipitate a relapse to drug taking behaviors. Thus, propranolol might be an effective treatment to prevent the occurrence of such anxieties and conditioned withdrawal reactions. The present results indicate that, in addition, β-adrenergic antagonists may alleviate somatic symptoms and other aversive components of opiate withdrawal. The constellation of these effects indicates that these agents may be beneficial in helping addicts overcome their opiate dependency. It is hoped that future research efforts might be directed to test these hypotheses in opiate-addicted individuals.

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