Opioid Antagonist Affects Behavioral Effects of Exposure In Vivo

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This study tested the hypothesis that endogenous opioids are involved in the extinction of phobic fear through exposure in vivo. Forty-eight spider phobics participated in a 2-hr therapist-directed exposure in vivo treatment. Sixteen Ss were assigned to placebo, 16 to a low dose of naltrexone, and 16 to a high dose of naltrexone. Before intervention, after treatment, and at a 1-wk follow-up test, self-report, physiological, and behavioral measures of phobic fear were completed. At 1-wk follow-up, naltrexone was significantly related, in a dose-dependent way, to a greater relapse on avoidance measures but not on emotional, cognitive, and physiological measures. Endogenous opioids may be specifically involved in the extinction of avoidance behavior but not in the extinction of all aspects of phobic fear.

There is evidence that endogenous opioids, which are released during anxiety, play a role in the extinction of phobic fear. In human species, it has been demonstrated that opioid agonists impede extinction of classically conditioned fear (Celley, 1987). In humans, a strong negative correlation between state anxiety and endogenous opiates in cerebrospinal fluid has been found (Post, Pickar, Ballenger, Naber, & Rounsaville, 1984). This finding is consistent with the idea that endogenous opioids reduce anxiety. However, the correlational nature of this study precludes any firm conclusions. Experimental studies, using pharmacological manipulation of the endogenous opioid system, have yielded more evidence for a causal role. Ilanga, Carr, Hunt, and Adamson (1988) demonstrated that naloxone (an opioid antagonist) rendered the effects of systematic desensitization for various simple phobias ineffective. Likewise, De Ruzza, Taylor, Boltwood, and Götestam (1991) demonstrated that naltrexone (also an opioid antagonist) impeded approach of spider phobics during a behavioral approach task and was related to higher heart rate (HR) and subjective anxiety during the step in which subjects began to drop out of the approach test.

These findings indicate that endogenous opioids play a role in the extinction of phobic fear. However, the precise mechanism is largely unknown. At least two processes can be hypothesized. One possibility is that endogenous opioids directly attenuate anxiety, by means of a negative feedback loop: Anxiety causes (with some delay) their release, which causes attenuation of anxiety. This theory would (at least partially) account for the typical habituation curves of subjective anxiety and physiological parameters observed during prolonged exposure in vivo (Foer & Kozak, 1986). At a conceptual level, this theory can be expressed in terms of Solomon’s opponent-process theory, which assumes that an emotional process (“A”) evokes a second process (“B”), which opposes the first process, so that the net effect is the sum of the two processes (Solomon, 1980).

A second possibility is that endogenous opioids do not directly decrease anxiety in general but affect specific dimensions of phobic fear. More specifically, endogenous opioids might lead to a euphoric state (as morphine does), which might be experienced by the person independently from anxiety. In this case, endogenous opioids would promote approach behavior and courage by giving these behaviors a pleasant aspect, despite the experience of anxiety. Consequently, a long-term effect would be that future approach behavior is facilitated because it has been reinforced by the pleasant emotional experience of the endogenous opioid release (Egan et al., 1988; Merluzzi et al., 1991). This possibility is in line with theories stressing the relative independence of positive and negative emotions (e.g., Tellegen, 1985; Watson & Tellegen, 1985) and the relative independence of the experience of anxiety and courageous behavior (Rachman, 1984).

The present study aimed to further elucidate the role of endogenous opioids in the extinction of phobic fear by exposure in vivo. As in two previous studies (Egan et al., 1988; Merluzzi et al., 1991), the effects of endogenous opioids were manipulated by a pharmacological antagonist. One previous study (Egan et al., 1988) did not look directly at exposure but used systematic desensitization and studied a heterogeneous sample of simple phobics. As in one other previous study (Merluzzi et al., 1991), the present study examined the influences of endogenous opioids on exposure in vivo in a homogeneous sample of simple phobics (spider phobics) on several dimensions of phobic fear (i.e., approach behavior, subjective emotional and cognitive dimensions, and physiological reactions). There are three important differences between the Merluzzi et al. study and the present study. First, in contrast to the Merluzzi et al. study, exposure time was prolonged and standardized (2 hr). Moreover, in the Merluzzi et al. study, the therapist gave minimal
support and avoided modeling the exercises, two actions that were used in the present study to achieve maximum exposure. Thus, the Merluzzi et al. study seems to be more representative of a free-access test, whereas our study seems to be more akin to the forced extinction procedures that are used in animal research. Second, the present study was directed toward investigating both short-term and long-term effects of endogenous opioids on reduction of phobic fear by measuring effects immediately after treatment and at a 1-wk follow-up (when opioid blockers are no longer active). Third, the present study was directed toward investigating the effects of different dosages of the opioid antagonist. It was reasoned that if endogenous opioids are involved in the extinction of phobic fear, the extent of their influence would depend on the degree to which their activity is blocked.

Method

Subjects

The final sample consisted of 48 female spider phobics from all over Holland, selected from 119 persons who applied for treatment at the university spider phobia project. Exclusion criteria were male sex, pregnancy, liver or kidney dysfunction, previous liver or kidney disease, use of opiate medication, and addiction to drugs or alcohol. For inclusion, subjects had to meet the criteria of the Diagnos tics and Statistical Manual of Mental Disorders (3rd ed., rev., American Psychiatric Association, 1987) for simple phobia, with spider phobia as their main psychopathological problem, and subjects had to sign an informed consent form including a statement that they would return for the second session, even if they had not profited from the first session or felt completely cured after the first treatment. One subject of the low-naltre
toxone-dose condition got sick and could not fully participate in the exposure treatment. She was excluded from the study and replaced by a new subject. The mean age in the final sample was 28.5 years (SD = 8.9), and the mean educational level—on a scale ranging from only primary school (1) to finished university (9)—was rather high (mean = 6.1, SD = 1.5). All reported that fear of spiders had been acquired before the age of 13 years. Mean Spider Phobia Questionnaire (SPQ; Kla rman, Weerts, Hastings, Melamed, & Lang, 1974) score was 22.3 (SD = 4.3). This is comparable to the mean SPQ score of spider phobics in previous studies (in Öst, Salkovskis, & Hellström, 1991, M = 20.8 and SD = 3.7; in Arntz & Lavy, 1992, M = 23.4 and SD = 3.2) and considerably higher than the mean SPQ score of normal women (N = 50, M = 5.6, SD = 5.5; Arntz & Lavy, 1993).

Materials and Assessment

Self-report questionnaires. The following questionnaires were used to assess various aspects of spider phobia: (a) the Spider Phobia Questionnaire (SPQ), a 31-item questionnaire developed by Kla rman et al. (1974; see also Fredrickson, 1983; range of scale = 0–31), which has proved to be a reliable instrument in our previous research (Cronbach’s alpha = .88); (b) the two main phobia subcales of the Fear Questionnaire (FQ; Marks & Mathews, 1979), assessing subjective fear and avoidance of the most feared situation, which must be described by the respondent (range of both scales = 0–8); (c) the Spider Belief Questionnaire (SBQ), an instrument measuring the strength of belief in various (irrational or unrealistic) ideas about both spiders and the self during confrontation with a spider. The SBQ presents ideas observed to be spontaneously expressed by spider phobics during exposure treatment (Arntz, Lavy, van den Berg, van Rijnsoort, in press). Examples of spider-related beliefs are “the spider will attack me” and “the spider smells that

I’m anxious.” Examples of self-related beliefs are “I will lose control” and “I will become crazy.” Most self-related beliefs resemble those often held by panic patients. The subject is instructed to indicate the strength of each belief as experienced during confrontation with a spider by filling in a percentage (0% to 100%). We obtained two scores: (a) the mean strength of the spider-related beliefs (0–100; Cronbach’s alpha = .94) and (b) the mean strength of the self-related beliefs (0–100; Cronbach’s alpha = .92).

Behavioral measures. A behavioral approach test (BAT) was used to assess avoidance of spiders. During the BAT, the subject was seated in a chair in a dimly lit, sound-attenuated room. A large shelf (3-m long) was placed in front of the subject. On the side opposite the subject, a glass jar containing a medium-sized live house spider was placed on a platform that could be advanced by the subject by means of a string. The subject was instructed to advance the jar up to the point at which she could tolerate without forcing herself. Distance was scored as follows: 300 cm = 0; 300 cm to 150 cm = 1; 150 cm to 75 cm = 2; 75 cm to 37.5 cm = 3; 37.5 cm to 19 cm = 4; 19 cm to 0 cm = 5. The subject was instructed to try the following steps after 0 cm had been reached (BAT score in parentheses): touch the jar (6); open the jar (7); touch the spider with a pencil (8); put the spider with the pencil in a basin (9); touch the spider with a pencil (10); touch the spider with a finger (11); and take the spider on her hands (12). Thus, successive BAT steps were coded in terms of a 13-point scale. Subjective anxiety experienced during the BAT was measured with a 100-mm visual analogue scale (VAS) ranging from completely relaxed (0 mm) to extreme panic (100 mm). The rating was measured in millimeters.

Physiological measures. During the BAT, skin conductance level (SCL) and HR were continuously measured. SCL was measured with two Beckman silver-silver chloride electrodes (8-mm diameter), placed on the medial phalanges of the second and third fingers of the subject’s nondominant hand. The electrodes were filled with an isotonic paste and were connected to a Beckman Skin Conductance Coupler (Type 9844), according to the method of constant voltage (0.5 V). The skin was cleaned with distilled water. HR was measured with disposable elec
trocardiograph electrodes (lead-II placement). The electrodes were connected to a Beckman Voltage/Purpose/Voltage Coupler (Type 9885A). Mean SCL and mean HR were obtained during a 20-s baseline period (rest) before the BAT, during a 20-s period at the start of the BAT, and during a 20-s period at the end of the BAT.

Spiders. More than 30 spiders of various types and sizes were available to match the spiders that were used during the exposure exercises to the specific fears of each subject and to guarantee a hierarchical exposure procedure.

Procedure

Design and pharmacological manipulation. There were three conditions (n = 16 each): placebo, low dose of naltrexone (25 mg), and high dose of naltrexone (100 mg). According to the American College of Medical Toxicology (AHFS) Drug Information (AHFS, 1989), the peak plasma concentration of naltrexone usually occurs within 1 hr of oral administration. Approximately 4 hr after administration, the naltrexone plasma concentration drops to 50% of the peak value. The major metabolite, 6-β-naltrexol, is also an opiate antagonist and reduces plasma concentration within 2 hr of administration. Four hours after administration, its concentration drops to 79%. A single dose of naltrexone may have opiate-antagonistic effects for as long as 24 hr. On

1 Flooding, though, might be considered as an even better anal\nogical forced extinction as used in animal research. However, note that present therapeutic approach did use floodinglike procedures, in subjects were pressed to execute exercises that evoked prolonged levels of anxiety.
basis of pharmacological information and consultancy of the university hospital pharmacist, we decided to use 25 mg of naltrexone as a low dose and 100 mg as a high dose. Treatment started 1.5 hr after administration and continued for 2 hr. The low dose was presumed to partially block endogenous opioid activity; the high dose, to block it for the most part.

All therapists, assistants, and researchers were unaware of pharmacological condition. The hospital pharmacist revealed the pharmacological status of each subject after the study was finished. Placebo, low, and high doses of naltrexone were administered with capsules that had to be swallowed. To balance the therapists over the three conditions, codes were given to the three types of capsules. Only one researcher (Arnoud Arntz) knew these codes (without knowing their meaning) and allocated therapists to conditions. Subjects were randomly allocated to one of the three conditions.

We measured dependent variables on four occasions: pretest (before drug administration); posttest (following the first treatment session); 1-wk follow-up test (before the second treatment session); and a second follow-up test (after the second treatment session). There was no pharmacological manipulation during the second session. The second treatment session was given for ethical reasons and to explore possible long-term negative effects of naltrexone on later (drug-free) exposure.

Therapists and treatment. Therapists were 6 advanced students in mental health sciences who had been trained extensively by therapists experienced in giving the one-session therapist-directed exposure treatment as developed by Ost (1989). Just before treatment started, the therapist thoroughly explained to the subject the role of avoidance in maintenance of the problem and the in vivo exposure treatment. It was stressed that treatment would be hard but that if the subject would be courageous and execute the anxiety-evoking exercises, fear would decrease. Fear-relevant conditions were clarified to ensure a hierarchical approach. Treatment consisted of exposure exercises (ranging from looking at a spider to touching the basin that contained the spider to touching the spider with a pencil to touching it with a finger; and finally to having the spider walk on the hands or other body parts). During treatment various spiders were used in a hierarchical way. Hierarchies were based on the subject's individual fear and could incorporate aspects such as the spider's color, size, or species. Exercises generally evoked high levels of anxiety, and the therapist's role was to encourage the subject to continue the exercise until fear was reduced to an acceptable level. If the subject was able to do the exercise with a level of anxiety acceptable to the person, the next exercise was started. The therapist modeled the exercise briefly if it seemed clinically indicated, only to demonstrate the exercise and to motivate the subject to do the exercise herself. Each therapist treated an equal number of subjects in each condition. Both sessions started with those exercises with which the subject indicated she was able to start. For most subjects, a 2-hr exposure session brings about a considerable reduction of fear, but not a complete cure (Arntz & Lavy, 1993).

Procedure. Subjects were tested and treated individually at the university. Before participating in the study itself, subjects were examined by a physician to exclude those at risk with the pharmacological manipulation. After signing a consent form, subjects filled in the SPQ, PQ, and SBS. Next, an assistant conducted the subject to a psychophysiological recording room. Before starting with the BAT, SC and HR electrodes were fastened to the subject. Next, the subject was instructed to relax and was left alone. Approximately 10 min later baseline measurements of HR and SC were obtained, and the experimenter returned and instructed the subject that during the BAT she should approach the spider as far as she could tolerate, without forcing herself. Next, the steps of the BAT were explained. A jar containing the spider was brought into the room and placed at maximal distance, and the subject was left alone. The subject was instructed to start her approach after a signal that was given through the intercom (in order to measure physiology at the start of the task) and to indicate maximal approach by raising a hand (which could be seen by the assistant through a one-way screen). After 100 s of maximal approach, the assistant returned and asked the subject to rate anxiety on theVAS.

After pretest assessment, the subject swallowed the capsule in the presence of the assistant and rested until the exposure treatment started. Just before exposure treatment started, a thorough explanation of its rationale was given, questions of the subject were answered, and the main dimensions of the subject's fear were clarified. It was also made clear to the subject that she would not be forced to do things against her will. Treatment lasted 2 hr. Following the first exposure session, the subject rested for one-half hour before filling in the posttest questionnaires and participating in the BAT. The importance of returning the next week for the second session was stressed before the subject left.

The second session was given exactly 1 week after the first session at the same location. Before the second session, subjects filled in the questionnaires and participated in the BAT (1-week follow-up test). Next, the second treatment session was given by a different therapist, following the same format as the first treatment session. After this, questionnaires and BAT were repeated, and the subject was instructed about maintenance exercises and thanked for participating.

Results

Pretest Differences

Analyses of variance (ANOVAs) on age, level of education, and pretest dependent variables yielded nonsignificant condition effects (all Fs < 1).

Dropouts

Two subjects, 1 in the placebo condition and 1 in the low-dose condition, did not return for the second session. Inspection of their data revealed that they had not improved during the first treatment session. Excluding them would have resulted in a biased therapeutic effect of the placebo and low-dose conditions. Therefore, the missing data at both tests of the 2nd week were estimated by extrapolating the scores of the 1st week posttest. It should be noted that analyses with and without these 2 subjects led to identical conclusions. In the analyses presented below, missing data were estimated.

Effects of the Pharmacological Manipulation

The effects of naltrexone were tested through analyses of covariance (ANCOVAs) performed on the first session posttest and the 1-week follow-up (second session pretest) measures, with the relevant first session pretest variable as covariant. The dose effect was tested by polynomial contrasts, the first testing the linear effect of the naltroxone dose and the second testing the linearity assumption (i.e., testing whether there was any quadratic dose effect, which would indicate deviation from linearity). The linear dose effect was considered as the essential test of the hypothesis. Before the ANCOVAs were executed, the assumption of parallel regression slopes was tested. None of these tests were significant (ps > .10).2

2 As an additional check of the validity of the ANCOVAs, ANOVAs on change scores were performed. These yielded results similar to those of the ANCOVAs.
Self-report scales. As is shown in Figure 1, the mean SPQ scores showed a parallel decrease from pre- to posttest of Session 1. The ANCOVA yielded nonsignificant dose effects (Table 1). Similarly, at the pretest of the second session (1-week follow-up), differences between conditions were nonsignificant (Table 1).

The fear ratings of the main phobic situation (FQ fear) showed a pattern similar to that of the SPQ; parallel changes in all three conditions (Table 1). The avoidance rating of the FQ main phobia item showed a different pattern: parallel decreases from pre- to posttest of the first session, but a somewhat larger relapse at the follow-up test 1 week later in the high-naltrexone-dose condition. The linear dose-response contrast was marginally significant (p = .06; Table 1). There was no significant deviation from the linear dose effect at this test. Spider-related and self-reported ratings as measured by the SBQ showed the same pattern as the SPQ: parallel changes in all three conditions; drug effects were nonsignificant (Table 1).

Behavioral Approach Test. The BAT appeared to be most clearly influenced by naltrexone. At the posttest of the first session, subjects in the high-naltrexone-dose condition appeared to perform worse than did those in the placebo condition (Figure 1), though the effect failed to reach significance (p = .09; Table 1). At the 1-week follow-up, there was a significant negative linear dose effect of naltrexone (p = .025; see Figure 1 and Table 1). The quadratic dose effect was nonsignificant.

The subjective anxiety VAS ratings of the BAT exhibited parallel changes in all three conditions: Dose effects were nonsignificant (Table 1). Because these VAS ratings are contaminated by the different levels of approach that subjects reached, the scores were adjusted for approach by multiplying them by a distance score (13 = BAT approach score). A similar procedure has been used by Whitehead, Blackwell, and Robinson (1978). No significant effects emerged, however.

Physiology. Physiological parameters obtained during the BAT were expressed as change scores with respect to baseline levels (ΔHR, ΔSCL). At each test there were significant increases in HR from baseline to maximum approach (mean ΔHRs = 11.3, 10.7, 9.7, and 9.1 for the 4 BATs; t(47) > 4.5, p < .0001; mean ΔSCLs = 2.54, 2.01, 1.23, and 0.97 for the 4 BATs; t(47) > 5.3, p < .0001). ANCOVAs with the pretest change score as covariate yielded nonsignificant naltrexone effects on ΔSCL and ΔHR at maximum approach (see Table 1; the direction of the linear effect is opposite to that hypothesized). SCL and HR were also obtained at the start of the BAT. ANCOVAs showed that naltrexone effects were identical to those obtained with physiological parameters at maximum approach.

Main Treatment Effects

ANOVA on the change scores between pretest and the three other tests revealed significant main effects of treatment on all self-report and behavioral measures, F(4, 47) > 35; p < .001, with the exception of the follow-up VAS rating of anxiety experienced during the BAT, which showed a smaller decrease, F(4, 47) = 4.99, p = .03. At the start of the BAT, ΔHR was also significantly lower at the three posttests than at the pretest, F(4, 47) > 4.98, p < .03. However, ΔSCLs at start and at maximum approach, and ΔHR at maximum approach, did not decrease significantly over time. It should be noted that both the VAS ratings and the physiological parameters at maximum approach were contaminated by differences in approach during the four BATs. In sum, most measures indicate that the exposure treatment was very effective.

Further Exploration

In the ANCOVAs, the dose-effect relationship was tested with polynomial contrasts with equal spacing between doses. It might be argued that taking into account the objective differences among the naltrexone doses (0 mg, 25 mg, and 100 mg) in the polynomial contrasts would be a more valid procedure.
Table 1

<table>
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<tr>
<th>Measure and effect</th>
<th>Session 1 posttest</th>
<th>Session 2 posttest (follow-up)</th>
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<tr>
<td></td>
<td>t(44) p</td>
<td>t(44) p</td>
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<tr>
<td>SPQ</td>
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<tr>
<td>lin</td>
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<td>qua</td>
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<td>lin</td>
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<tr>
<td>qua</td>
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<td>FQ—Avoidance</td>
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<tr>
<td>lin</td>
<td>1.00 .32</td>
<td>1.92 .06</td>
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<tr>
<td>qua</td>
<td>-0.40 .69</td>
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<td>1.13 .26</td>
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<tr>
<td>qua</td>
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Note. lin = linear naltrexone dose effect; qua = quadratic naltrexone dose effect (deviation from linearity). Skin conductance level (SCL) and heart rate (HR) were measured at maximum approach and expressed as change scores from baseline (ASCL, AHR). SPQ = Spider Phobia Questionnaire; FQ = Fear Questionnaire; SBQ = Spider Belief Questionnaire; BAT = Behavioral Approach Test.

The main finding of the present study is that naltrexone was related (in a dose-dependent way) to a greater relapse on a 1-week follow-up approach test after an intense 2-hr exposure treatment. On the only other measure of the approach—avoidance dimension, the main phobia avoidance rating of the FQ (FQ—Avoidance), an identical effect was found, though of borderline significance (p = .06). On all other dimensions there appeared to be no significant effect of naltrexone. There are several ways in which these results can be interpreted. First, naltrexone might have influenced exposure by pharmacological effects other than blocking the endogenous opioid system. However, one might raise the objection that in that case a general negative effect of naltrexone would have been more probable than a specific effect. Second, the size of the naltrexone effect on the BAT is not impressive in a statistical sense and would not reach significance if experimentwise, rather than responsewise, Bonferroni corrections were applied. Thus, the specific effect of naltrexone might be an accidental finding. Third, some measures may be relatively insensitive to the drug effects, or the cell sizes may have been too small. However, other researchers have found negative effects of opioid blockers on subjective and physiological measures using tests with fewer degrees of freedom. Furthermore, most measures appeared to be very sensitive in detecting changes that were due to treatment. Moreover, on various measures there was not even a trend toward significance (e.g., SPQ), or the effect was in a direction opposite to that hypothesized (HR, SCL). Fourth, it could be hypothesized that treatment failed to evoke high levels of anxiety, because it was too supportive and because too much modeling was used, so that endogenous opioids were not released during treatment. However, given the way treatment was executed, it seems unlikely that it did not evoke high levels of anxiety: Therapists put considerable pressure on subjects to do the exposure exercises, which generally evoke high levels of fear.

Finally, a theoretical interpretation might be that endogenous opioids are not necessary for the extinction of phobic fear. The present study suggests that, even with a high dose of naltrexone, all aspects of phobic fear may decrease with prolonged exposure. The present results are in line with the view that endogenous opioids stimulate and reinforce approach behavior but do not directly influence other phobic dimensions.

Yet how can this view explain that naltrexone was not significantly related to approach immediately after the first treatment? Possibly approach behavior immediately following the therapist-directed exposure was governed relatively strongly by rules learned and social reinforcement given by the therapist during treatment. At the follow-up test, these influences might have weakened, and approach behavior might have been more influenced by its emotional valence. Thus, the better retention of approach behavior at follow-up in the placebo condition might be explained by the more positive valence this behavior has acquired through reinforcement by previous endogenous opioid release.

To summarize, the present study seems to provide more evidence for the hypothesis that endogenous opioids affect the behavioral system than for the view that they play a direct role in the extinction of phobic fear in general. However, several al-
ternative interpretations cannot be ruled out. Moreover, on the basis of studies conducted to date, it seems impossible to determine whether the negative effects of opioid blockers on subjective and physiological anxiety indexes, as observed in previous studies, are a direct consequence of opioid blocking or a secondary effect of less exposure, because the opioid antagonist impedes approach behavior. Clearly, further research is needed to clarify this issue.

References


Received May 18, 1992
Revision received November 13, 1991
Accepted November 19, 1992