Presentation of a distractor speeds the decay of a pentobarbital-insensitive nonopioid hypoalgesia in rats

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Higher psychological/neural processes are thought to be involved in brief, but not long, shock-induced hypoalgesia. Researchers have shown that three brief (0.75-sec) tailshocks produce a hypoalgesia that is eliminated by spinalization, decerebration, pentobarbital anesthesia, and a postshock distractor. In contrast, three long (25-sec) tailshocks produce a hypoalgesia that is eliminated by spinalization but not decerebration. Although it has been assumed that this hypoalgesia would survive pentobarbital anesthesia and exposure to a distracting stimulus, this has not been previously tested. Experiment 1 demonstrates that pentobarbital has no effect on long shock-induced hypoalgesia. Contrary to our expectations, this nonopioid hypoalgesia was attenuated by a postshock distractor (Experiment 2). This distractor effect appears to be opioid mediated because it was blocked by naltrexone (Experiment 3) and a low dose of morphine effectively substituted for the distractor (Experiment 4). The role of memorial processing in hypoalgesia is discussed.

Animals exposed to an aversive event often exhibit a reduction in pain reactivity, a phenomenon known as hypoalgesia. For example, exposure to three mild (0.75-sec 1.0-mA) shocks can produce a hypoalgesia in rats that lasts 10 min or more (Grau, 1984; Meagher, Grau, & King, 1989). This hypoalgesia attenuates both supraspinally (e.g., formalin-induced recuperative behavior [the "formalin test"]) and spinally mediated (e.g., tail-withdrawal from radiant heat [the "tailflick test"] measures of pain reactivity (Fanselow, 1984; Grau, 1984)). Importantly, we have shown that the reduced pain reactivity observed on the tailflick test does not reflect a general disruption in either sensory processing or motor reactivity: at the same time points where subjects are unresponsive to painful radiant heat, they exhibit normal or enhanced reactivity to tactile stimulation (Illich & Grau, 1990).

Our early studies of this phenomenon focused on the hypoalgesia observed on the tailflick test after three brief (0.75-sec) 1-mA tailshocks (Grau, 1984, 1987a, 1987b; Meagher, Grau, & King, 1989, 1990). A summary of our findings is presented in Figure 1 under the heading Brief Shock. Because the opioid antagonist naltrexone has a very different impact on this hypoalgesia depending upon when pain reactivity is tested (Grau, 1987a), this column has been subdivided into two columns, one for 2 min after shock and one for 6–10 min after shock. At the 2-min time point, the hypoalgesia is naltrexone-insensitive, or nonopioid, in form, whereas at 6–10 min after shock, the hypoalgesia is naltrexone-reversible, or opioid, in nature (a similar pattern of results is obtained if subjects are made tolerant to morphine; see Grau, Biles, & Illich, 1991). Given this, we have suggested that three brief shocks elicit a transient nonopioid hypoalgesia followed by a long-lasting opioid hypoalgesia (Grau, 1984; Grau, Biles, & Illich, 1991). Both of these hypoalgesic responses are eliminated by a high-level spinal transection (at the second thoracic vertebrae, T2), which suggests supraspinal systems play a critical role (Meagher et al., 1990). Indeed, the hypoalgesia is also eliminated by decerebration (Meagher et al., 1990), lesions of the frontal cortex (Meagher et al., 1989), and pentobarbital anesthesia (Grau, 1987a), a pattern of results that has led us to propose that the hypoalgesia depends on forebrain mechanisms (for further evidence on this issue, see Chance, 1980, Fanselow, 1986, and Maier, 1989).

We (Grau, 1987a, 1987b; Grau, Illich, Chen, & Meagher, 1991), and others (Maier, 1989), have suggested that learning and memory play a critical role in producing the hypoalgesia observed after a brief exposure to shock. Specifically, we argued that the "central representation" of the aversive event in working memory acts to maintain the activation of the hypoalgesic systems. If this is true, then the presentation of an unexpected "distractor" after shock should displace the representation of shock from working memory and cause the hypoalgesia to decay more rapidly (for a detailed derivation of these predictions, see Grau 1987a, 1987b). Supporting this, we have shown that a postshock distractor (a 1-min flashing light) causes both the nonopioid and opioid hypoalgesic responses to decay more rapidly (Grau, 1987a). (For other evidence supporting the memorial perspective, see Grau, 1987a, 1987b).
Figure 1. The impact of seven different experimental manipulations on the hypoalgesia observed 2 min or 6-10 min after brief shock or 2-10 min after long shock. The markers within each cell indicate whether the experimental manipulation had no effect (horizontal bar), attenuated the hypoalgesia (downward arrow), or potentiated the hypoalgesia (upward arrow). Question marks indicate cells that have not been previously tested.

1987b, Netto, Siegfried, & Izquierdo, 1987, and Maier & Keith, 1987.) We have also shown that a pharmacological manipulation that is known to disrupt memory (administration of scopolamine) eliminates brief-shock-induced hypoalgesia (Grau, Illich, et al., 1991). (Scopolamine also alters pain reactivity through nonmembrane mechanisms; for more information, see Grau, Illich, et al., 1991, Feigley, Beakey, & Saynisch, 1976, and Watkins, Katayama, Kinscheck, Mayer, & Hayes, 1984.)

When we originally outlined our theory, it was clear that some hypoalgesic effects do not depend on higher psychological/neutral systems. For example, Watkins and Mayer (1982) had shown that exposure to relatively severe footshock elicits a hypoalgesia that is eliminated by spinal transection but not decerebration (Watkins, Cobelli, & Mayer, 1982; Watkins, Kinscheck, & Mayer, 1983). These findings led Watkins and Mayer (1982, 1986) to suggest that the afferent nociceptive information was “directly” activating a hypoalgesic system at the level of the brainstem. Learning and memory presumably played little role in the production of this hypoalgesic effect. Instead, from this perspective, the magnitude and time course of the hypoalgesia is a simple function of shock severity; the greater the shock severity, the stronger and more long lasting the hypoalgesia (Terman, Shavit, Lewis, Cannon, & Liebeskind, 1984).

We extended this basic notion and suggested that shock severity may also determine whether hypoalgesia depends on higher psychological/neutral mechanisms (Grau, 1987a; Grau, Burks, Kallina, King, & Meagher, 1995; Meagher et al., 1990). Our basic hypothesis was that the lower level modes of activation were directly engaged by long and/or intense shocks, while higher psychological/forebrain processes mediated the hypoalgesia observed after brief mild shocks. To test this notion, we assessed the impact of increasing shock severity by simply increasing the duration of the shocks from 0.75 to 25 sec. A summary of our results is presented in Figure 1 under the heading Long Shock. We found that three long (25-sec) 1.0-mA tailshocks produced a hypoalgesia that was eliminated by spinal transection but not decerebration or lesions of the frontal cortex (Meagher et al., 1989, 1990). In fact, decerebration actually potentiated the hypoalgesia, a finding that suggests the operation “released” the hypoalgesic system from a source of tonic inhibition. We also tested the form of the hypoalgesia observed in decerebrated and sham-operated rats. It proved to be naltrexone-insensitive, or nonopioid, in form, and this was true over the entire 10 min of testing (Meagher et al., 1990). Finally, we tested the impact of the cholinergic antagonist scopolamine. Given that forebrain systems appeared to inhibit the activation of this nonopioid mechanism, and that cholinergic systems have been frequently implicated in similar inhibitory effects (Thomas, 1988), we hypothesized that scopolamine might potentiate the hypoalgesia. We found that scopolamine did indeed potentiate long-shock-induced hypoalgesia (Grau, Illich, et al., 1991). Given these findings, we have argued that the afferent nociceptive information directly activates a nonopioid hypoalgesic system at the level of the brainstem (Meagher, Chen, Salinas, & Grau, 1993; Meagher et al., 1990). Similarly, Maier (1989) has reported that five 5-sec 1-mA tailshocks produces a pentobarbital-insensitive, nonopioid, hypoalgesia on the tailflick test. He too has argued that this hypoalgesic effect reflects a simple unconditioned response to shock, one that does not depend on learning or memory.

Given the theories outlined by our laboratory (Grau, 1987a, 1987b; Grau, Illich, et al., 1991; Meagher et al., 1993) and by Maier (1989), one would expect that the hypoalgesia observed after three long tailshocks should survive both pentobarbital anesthesia and exposure to a postshock distractor. Indeed, because other manipulations that disrupt memorial processing (administration of scopolamine) and forebrain functioning (decerebration) potentiate this hypoalgesia, one might expect to find that these manipulations actually potentiate the nonopioid hypoalgesia observed after three long shocks. We addressed these issues by testing the impact of pentobarbital anesthesia (Experiment 1) and the presentation of a postshock distractor (Experiment 2). Contrary to our expectations, the distractor attenuated the hypoalgesia. In Experiments 3 and 4, we explored the mechanism that mediates this effect.

**GENERAL METHOD**

**Subjects**

The subjects were male Sprague-Dawley rats obtained from Harlan (Houston, TX). They were 100-120 days old and weighed between 420 and 520 g. The animals were individually housed and maintained on ad-lib food and water. They were maintained on a 12:12-h light:dark cycle, and behavioral testing occurred during the last 4 h of the light cycle.
Apparatus
During behavioral testing, the rats were restrained in one of two Plexiglas tubes (22 cm length, 6.8 cm internal diameter). Tail-shock was provided by a 660-V transformer that provided a constant-current 1.0-mA shock. The shock electrodes were constructed from a modified fuse clip and were lightly coated with electrode paste. The electrode was taped to the rat’s tail, approximately 15 cm behind the rear of the tubes. Pain reactivity was assessed using a radiant heat tailflick device. A detailed description of this device, as well as other details of the apparatus, can be found elsewhere (Grau, 1984, 1987a; Meagher et al., 1993; Meagher et al., 1990).

Procedure
All subjects were randomly assigned to experimental conditions and placed in restraining tubes for a 15-min acclimation period. They then received four baseline tailflick tests at 2-min intervals. An 8-sec cutoff was used in order to prevent tissue damage. The last three tests were used to compute the subject’s baseline level of pain reactivity. After the last tailflick test, the electrodes were attached to the rat’s tail with adhesive tape. In all the experiments, one half of the subjects in each experimental condition then received three 25-sec 1.0-mA shocks at 20-sec intervals. The remaining subjects were treated the same except that shock was withheld. Two minutes after shock termination, or an equivalent period of restraint, the rat’s tail was untaped and pain reactivity was tested five times at 2-min intervals.

Statistical Analyses
Analyses of variance (ANOVAs) were performed on both the baseline and the postshock tailflick data. Post hoc comparisons of the group means were made with the Newman-Keuls test.

EXPERIMENT 1

Researchers have generally used two manipulations to explore the role of forebrain systems in environmentally induced hypoalgesia: decerebration and pentobarbital anesthesia. In a prior study, we showed that decerebration potentiates the hypoalgesia observed after three long shocks, suggesting that the operation releases the nonopioid system from descending inhibition (Meagher et al., 1990). Experiment 1 tested whether pentobarbital anesthesia has a similar potentiating effect.

Method
The experiment involved a 2 (drug) × 2 (shock) factorial design (n = 6). Half of the subjects were injected (i.p.) with 45 mg/kg of sodium pentobarbital (V-Pento; distributed by A-J Buck & Son) and returned to their home cages for a 20-min interval, as described by Grau (1987a). The other subjects were similarly treated, with the exception that they received an injection of saline instead of pentobarbital. Prior to testing, we verified that the pentobarbital-treated rats were in a flaccid state of surgical anesthesia but were breathing normally and could exhibit a tailflick reflex. Half the subjects then received three 25-sec 1.0-mA shocks; the other half remained unshocked.

Results and Discussion
The results are depicted in Figure 2. Baseline tailflick latencies are presented in the left corner of the graph. An ANOVA indicated that baseline tailflick latencies did not differ prior to shock treatment (all F < 2.71, p > .05). Tailflick latencies observed after shock are presented on the right side of the graph. Exposure to shock induced a strong hypoalgesia in both the saline- and the pentobarbital-treated groups. An ANOVA confirmed that shock had a significant impact [F(1,20) = 34.75, p < .001]. Neither the main effect of drug treatment nor its interaction with shock treatment approached statistical significance (both F < 1.09, p > .05). Although there was a significant trials effect [F(4,80) = 4.05, p < .01], the trials effect did not interact with any of the between-subjects treatments (all F < 1.0, p > .05). Post hoc comparisons showed that the two shocked groups were hypoalgesic relative to the unshocked controls. No other differences were significant.

Thus, long shock-induced hypoalgesia survives pentobarbital anesthesia as well as decerebration (Meagher et al., 1993; Meagher et al., 1990). However, unlike decerebration, pentobarbital anesthesia did not potentiate the hypoalgesia. If the potentiated hypoalgesia observed after decerebration reflects a release from tonic inhibition, pentobarbital must spare this inhibitory mechanism.

EXPERIMENT 2

We have previously shown that a postshock distractor causes the hypoalgesia observed after three brief (0.75-sec) shocks to decay more rapidly (Grau, 1987a). Experiment 2 tested whether a distractor has a similar effect on the hypoalgesia observed after three long (25-sec) shocks. Given the theories outlined by our laboratory (Grau, 1987a, 1987b; Grau, Illich, et al., 1991; Meagher et al., 1993) and by Maier (1989), one would expect that
memorial mechanisms are not involved in the production of this brainstem-mediated hypoalgesia and, consequently, that the distractor should have no effect.

Nevertheless, there are reasons to entertain the opposite hypothesis. We recently showed that a postshock distractor can speed the decay of hypoalgesia in spinalized rats (Grau, Salinas, Illich, & Meagher, 1990). If spinal systems exhibit memory-like effects, brainstem-mediated effects may also prove sensitive to distraction.

Method

The experiment involved a 2 (shock) × 2 (distractor) factorial design (n = 8). Immediately after the last shock, or an equivalent period of restraint, half the subjects in each condition experienced the light distractor for 1 min. In order to increase the salience of the distractor, it was flashed on (36 msec) and off (24 msec) during the exposure period, as described in Grau (1987a).

Results and Discussion

The results are depicted in Figure 3. It is evident that baseline levels of pain reactivity did not differ prior to shock (all Fs < 2.44, p > .05). Shock alone induced a strong hypoalgesia. Presentation of the distractor caused this hypoalgesia to decay more rapidly. An ANOVA confirmed that shock had a significant impact [F(1,28) = 12.01, p < .005]. Neither the main effect of distractor treatment nor its interaction with shock treatment were statistically significant (both Fs < 1.67, p > .05). The within-subjects terms revealed that there was a significant trials effect and that whether the distractor had an effect depended on the trial of testing (both Fs > 8.00, p < .001). The overall effect of shock treatment also varied across trials [F(4,112) = 4.57, p < .005]. Most importantly, the three-way interaction between test trial, shock, and distractor treatment confirmed that the time course of shock-induced hypoalgesia was modified by the presentation of the distractor [F(4,112) = 4.62, p < .01].

We found that the presentation of a distractor causes the hypoalgesia observed after three 25-sec tailshocks to decay more rapidly. Given that this basic effect has now been obtained with forebrain-mediated, brainstem-mediated, and spinally mediated hypoalgesic effects (Grau, 1987a; Grau et al., 1990), it is tempting to conclude that sensitivity to distraction represents a general property of pain modulatory circuits.

EXPERIMENT 3

Elsewhere, we have shown that the presentation of a distractor after three brief (0.75-sec) shocks not only speeds the decay of the hypoalgesia but it also modifies its form (Grau, 1987a). Specifically, we found that a postshock distractor alters the form of the hypoalgesia observed 2–4 min after shock, changing it from one that is naltrexone-insensitive to one that is fully naltrexone-reversible, or opioid, in form. Experiment 3 tested whether the presentation of a distractor has a similar impact on the hypoalgesia observed after three long (25-sec) shocks, changing it from one that is naltrexone-insensitive to one that is naltrexone-reversible. If it does, then naltrexone should eliminate the hypoalgesia that survives the distractor treatment.

Again, there is reason to anticipate the opposite outcome—that naltrexone may block the distractor effect. It is known that exposure to a novel stimulus, such as a distractor, can elicit some opioid release (Izquierdo & McGaugh, 1985, 1987; Netto et al., 1987; Rochford, 1992; Scallet, 1982). This is of interest because the opioid and nonopioid systems appear to be linked by a collateral inhibitory mechanism, so that the activation of one system inhibits the other (Grisel, Fleschner, Watkins, & Maier, 1993; Kirchgesner, Bodnar, & Pasternak, 1982; Steiman et al., 1990). Thus, the distractor may attenuate long shock-induced hypoalgesia because it elicits an opioid release that antagonizes the nonopioid hypoalgesia by means of collateral inhibition. If so, then blocking the opioid receptors with naltrexone should prevent the induction of collateral inhibition and, consequently, prevent the distractor from attenuating the hypoalgesia.

Method

The complete experiment involved a 2 (drug) × 2 (shock) × 2 (distractor) factorial design (n = 8). Half the rats were given an s.c. injection of naltrexone (14 mg/kg); the other half received saline. Although this is a high dose, which may preclude specification of receptor subtype, this dose was used in the prior studies (Grau, 1987a; Grisel et al., 1993), and comparisons across studies were of interest. After the injection, the subjects were placed in the restraining tubes for acclimation and baseline testing. Half the subjects then received three 25-sec 1.0-mA shocks; the other half re-
remained unshocked. Finally, half the subjects in each condition experienced the 1-min distracting stimulus, as described in Experiment 2.

Results and Discussion

The results are depicted in Figure 4. It is evident that baseline levels of pain reactivity did not differ prior to shock treatment (all $F_s < 1.0, p > .05$). In the absence of the distraction (upper panel), shock induced a strong, naltrexone-insensitive hypoalgesia. As expected, presentation of the distractor (lower panel) caused the hypoalgesia to decay more rapidly in saline-treated subjects.

The distractor had much less of an effect in subjects pre-treated with naltrexone.

An ANOVA confirmed that shock had a significant impact [$F(1,56) = 71.00, p < .001$] and that the impact of shock depended on distractor treatment [$F(1,56) = 6.35, p < .05$]. The main effect of distractor treatment was marginally significant [$F(1,56) = 3.45, p < .07$]. The remaining between-subjects terms did not approach statistical significance (all $F_s < 2.42, p > .05$). Post hoc comparisons indicated that shocked rats that did not experience the distractor and that naltrexone-treated rats that received the distractor were hypoalgesic, relative to the rats in the other five groups. No other differences were statistically significant.

The within-subjects terms showed that the change in tail-flick latencies observed across trials depended on distractor treatment [$F(4,224) = 2.62, p < .05$]. Most importantly, the three-way interaction confirmed that the effect of shock depended on both the trial of testing and the distractor treatment [$F(4,224) = 6.71, p < .001$]. There was also a significant drug $\times$ test trial interaction [$F(4,224) = 2.59, p < .05$]. The remaining within-subjects terms did not approach statistical significance (all $F_s < 1.96, p > .05$).

As reported elsewhere (Grau et al., 1995; Meagher et al., 1990), naltrexone did not attenuate the hypoalgesia observed after three long shocks. As found in Experiment 2, presentation of the distractor caused this non-opioid hypoalgesia to decay more rapidly. The distractor had less effect on shocked rats pretreated with naltrexone. This suggests that the distractor effect may depend on an opioid synapse, a synapse that could antagonize the nonopioid hypoalgesia by means of collateral inhibition (Grisel et al., 1993; Kirchgessner et al., 1982; Steinman et al., 1990).

EXPERIMENT 4

If the distractor attenuates long shock-induced hypoalgesia because it induces the release of an opioid, then other manipulations that activate this opioid system should have a similar effect. In Experiment 4, we explored this possibility by testing whether a postshock injection of an opiate (morphine), like a distractor, attenuates long-shock-induced hypoalgesia. Naturally, a very low dose (0.5 mg/kg) was used, one that should induce little hypoalgesia.

Method

The subjects were randomly assigned to four groups ($n = 8$). Half the subjects received three 25-sec 1.0-mA shocks; the other half served as the unshocked controls. Immediately after the last shock, or an equivalent period of restraint, half of the rats in each condition received either an s.c. injection of morphine (0.5 mg/kg) or saline while they remained in the restraining tubes.

Results and Discussion

The results are depicted in Figure 5. As can be seen, baseline tail-flick latencies did not differ among groups prior to shock treatment (all $F_s < 1.173, p > .05$). Explo-
sure to shock induced a strong hypoalgesia in the saline-treated rats (Group Shock–Sal). This hypoalgesia was reduced by an injection of morphine given after shock (Group Shock–Mor). An ANOVA confirmed that both the main effect of shock and the shock × drug interaction were significant (both $F_s > 7.00, p < .05$). The main effect of drug treatment was also statistically significant [$F(1,28) = 5.1, p < .05$]. The within-subjects terms revealed that there was a significant trials effect [$F(4,112) = 6.37, p < .001$]. The remaining within-subjects terms did not reach statistical significance (all $F_s < 2.35, p > .05$). Post hoc comparisons of the group means confirmed that the two shocked groups were hypoalgesic relative to the unshocked controls and that the difference between the two shocked groups was significant. No other differences were significant.

As predicted by the collateral inhibition model (Grisel et al., 1993; Kirchgesner et al., 1982; Steinman et al., 1990), postshock administration of morphine attenuated the nonopioid hypoalgesia elicited by long shock. Not only does this experiment extend the generality of the collateral inhibition model, it also addresses a limitation of a prior report. The problem is that Grisel et al. (1993) administered morphine before they stressed their subjects, and, consequently, the drug could have attenuated the impact of the stressor. This in turn could influence both the form and the magnitude of the hypoalgesia observed (Grau et al., 1995; Meagher et al., 1993; Terman et al., 1984). Experiment 4 avoided this interpretive problem by showing that morphine administered after shock antagonizes the nonopioid hypoalgesia elicited by long shock.

**GENERAL DISCUSSION**

The present study examined the impact of pentobarbital anesthesia and a postshock distractor on long shock-induced hypoalgesia. As expected, long shock-induced hypoalgesia survived pentobarbital anesthesia (Experiment 1). However, in contrast to decerebration, anestesia did not potentiate the hypoalgesia. A similar outcome was reported by Maier (1989) using five 5-sec tailshocks. In this regard, pentobarbital appears to have an effect that is more analogous to that produced by lesioning the frontal cortex, which neither potentiates nor attenuates long-shock-induced hypoalgesia. Elsewhere, we have argued that the septohippocampal cholinergic system may play a critical role in producing the potentiation effect (Grau, Illich, et al., 1991). Supporting this, we have shown that scopolamine potentiates long shock-induced hypoalgesia. Furthermore, septal lesions can potentiate both shock-induced and handling-induced hypoalgesia (Chance, 1980; Kelsey & Baker, 1983). According to this perspective, frontal cortex lesions fail to potentiate long-shock-induced hypoalgesia because they spare septal-hippocampal functioning. The dose of pentobarbital we used may have failed to produce potentiation for the same reason: it may have spared enough septohippocampal functioning to allow this system to maintain an inhibitory effect over the brainstem nonopioid system.

It is generally held (Grau, 1987a; Maier, 1989; Watkins & Mayer, 1982, 1986) that hypoalgesic effects that survive decerebration and/or pentobarbital anesthesia reflect the activation of pain inhibitory systems through lower level pathways. From this perspective, this hypoalgesia reflects an unconditioned response—one that does not depend on memorial processing. Accordingly, the magnitude and time course of the hypoalgesia observed after severe aversive stimuli should depend entirely on stimulus severity. Given this, we expected that a postshock distractor would not attenuate the brainstem-mediated hypoalgesia that we observe after three long tailshocks. Contrary to our expectations, Experiment 2 showed that a distractor causes long shock-induced hypoalgesia to decay more rapidly. This finding, together with our finding that a similar outcome can be obtained in spinalized rats (Grau et al., 1990), suggests that memory-like processing may occur at every level of the nervous system—that, at each level, the magnitude of hypoalgesia observed is primarily determined by the last event experienced. That this memory-like processing occurs for forebrain-mediated hypoalgesic effects is, in some ways, hardly surprising. What is remarkable, and what runs counter to prevailing theories (Grau, 1987a; Maier, 1989; Watkins & Mayer, 1982), is that this is also true.
for brainstem-mediated and spinally mediated hypalgesic effects. Interestingly, a similar principle appears to also determine judgments of pain in humans (Kahneban, Frederickson, Schreiber, & Redelmeir, 1993).

The results of Experiment 2 also have important methodological implications: they suggest that how subjects are treated after they experience shock may be a major determinant of the magnitude and duration of the hypalgesia observed and that this is true even though the hypalgesia is mediated at the level of the brainstem or spinal cord. Indeed, this variable may help to explain a number of discrepancies and anomalies. For example, a comparison of the nonopioid hypalgesia observed after shock schedules similar to the ones used in the present study reveals that the magnitude of the nonopioid hypalgesia observed varies tremendously (cf. Cannon, Terman, Lewis, & Liebeskind, 1984; Terman et al., 1984). Interestingly, researchers who report little hypalgesia repeatedly remove their subjects from the shock apparatus for testing—a manipulation that effectively exposes subjects to a variety of distracting stimuli. Conversely, we test subjects under conditions that should minimize exposure to extraneous stimuli and observe a much more robust hypalgesia. A similar analysis may help to explain an odd outcome noted by Liebeskind and his colleagues (Liebeskind, 1985). Using their usual testing procedure, which exposed subjects to a variety of distracting stimuli, they found that their hypalgesia decayed within about 10 min. Interestingly, no decay was observed if subjects were simply allowed to remain in the shock context undisturbed. Again, it appears that events that occurred after subjects experienced shock determined the time course of the hypalgesia observed.

We hypothesized that a novel distractor might attenuate the nonopioid hypalgesia observed after three long shocks because it induces the release of an opioid (Izquierdo & McGaugh, 1985, 1987; Netto et al., 1987; Rochford, 1992; Scallet, 1982). This is important because other evidence suggests that the opioid and nonopioid systems are linked by a form of collateral inhibition (Kirchgeissner et al., 1982). Even though the amount of opioid release may be insufficient to elicit hypalgesia (Experiment 2), it may be sufficient to inhibit the nonopioid system by means of collateral inhibition. If so, then preventing the opioid's action with naltrexone should prevent the distractor from attenuating the hypalgesia. The results of Experiment 3 were consistent with this prediction.

To further evaluate whether a collateral inhibition mechanism mediates the distractor effect, Experiment 4 examined the effect of giving rats morphine after shock. The morphine effectively substituted for the distractor and attenuated the hypalgesia. These findings both confirm and extend the results of Grisel et al. (1993), who reported that prior administration of morphine antagonizes the nonopioid hypalgesia elicited by environmental stressors. However, because Grisel et al. (1993) administered morphine before the animals were exposed to the stressors, morphine may have decreased the magnitude of the hypalgesia observed simply because it altered the perceived severity of these stressors. Our results help to refute this alternative explanation by showing that morphine given after the stressor has a similar effect.

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