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Extent and Control of Shock Affects Naltrexone Sensitivity of Stress-Induced Analgesia and Reactivity to Morphine

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HYSON, R. L., L. J. ASHCRAFT, R. C. DRUGAN, J. W. GRAU AND S. F. MAIER. *Extent and control of shock affects naltrexone sensitivity of stress-induced analgesia and reactivity to morphine.* PHARMAC. BIOCHEM. BEHAV. 17:(5) 1019–1025, 1982.—Opioid and nonopioid mediated changes in pain sensitivity have been observed after exposure to various stressful conditions. A series of inescapable shocks sequentially produces an early form of analgesia which is not affected by the opiate antagonist, naltrexone, and a late antinociceptive response which is sensitive to reversal by naltrexone. Here, this is shown to be true over a wide range of doses. In a further experiment subjects given either escapable or inescapable shock were analgesic immediately after the stress session. However, the analgesia of inescapably shocked subjects was more sensitive to reversal by naltrexone. A final experiment revealed that inescapably shocked subjects, but not escapably shocked subjects, were hyperreactive to the analgesic effects of morphine 24 hr after shock. These results suggest that activation of an opiate system occurs only after extended exposure to stress and that this activation is greater when the stress is inescapable. Implications for opioid versus nonopioid mechanisms of stress-induced analgesia are discussed.

Stress-induced analgesia Controllability Learned helplessness Morphine hyperreactivity
Inescapable shock Nonopioid pain inhibition Endogenous opiates

MUCH recent attention has been given to the physiological and psychological factors which are involved in pain inhibition mechanisms. Exposure to a variety of painful or stressful events results in a decrease in pain sensitivity/reactivity [4, 5, 7]. Study of this phenomena, called stress-induced analgesia, has primarily focused on the role of endogenous opiates in this antinociceptive response. Both electrical stimulation and opiate peptide microinjection into portions of the medial brainstem elicit analgesia [2, 22, 23]. It has been suggested [18] that endogenous opiates are released during stress and may inhibit pain via activation of this midbrain system. However, some forms of SIA have been found to be sensitive to reversal by opiate antagonists and cross-tolerant with morphine [3, 10, 25], while these manipulations have had little or no effect on other forms of SIA [1, 6, 8]. This has led to the conclusion that both opioid and nonopioid forms of SIA exist [5,16]. We will also use naltrexone reversal as a criterion for opioid vs nonopioid analgesia, although it should be recognized that nalxone, naltrexone, and morphine have high affinity for only the μ opiate receptors type [9,26]. Thus an effect termed as nonopioid may actually be opioid but at a different receptor type.

Given the likelihood that both opioid and nonopioid SIA can occur, it becomes important to determine what factors influence which form will be observed. The controllability/uncontrollability of the stressor may be a factor. Jackson, Maier, and Coon [15] reported that an extended series of inescapable shocks (80–5 sec shocks) sufficient to induce behavioral "learned helplessness" [21] produced an analgesic reaction upon brief reexposure to shock 24 hr later. An equivalent series of escapable shocks did not produce this long-term analgesic reaction. This inescapable shock produced analgesia was completely reversed by opiate antagonists [19] and completely cross tolerant with morphine [13]. In further support of the importance of escapability or controllability, Moye, Coon, Grau, and Maier [24] found that exposure to escapable shock either prior or subsequent to inescapable shock exposure blocked this long-term analgesia. Finally, Maier, Drugan, and Grau [20] found only inescapable shock to produce the more typical short-term SIA measured 30 min after the shock session. Escapable shock had relatively little effect on pain reactivity at this time point.

These data led Grau, Hyson, Maier, Madden, and Barchas [14] to argue that opiate analgesia systems might be activated by the organism's learning that it has no control over the inescapable shocks. If learning that shock is uncontrollable is important in triggering opiate-mediated SIA, then shock parameters (number and duration) should be critical. Many shocks over an extended period might be required for such learning to occur, thus accounting for the Lewis, Cannon, and Liebeskind [16] finding that a single 3 min continuous footshock produced only nonopioid analgesia, whereas 20 and 30 min of intermittent footshock leads to analgesia which appears opioid in nature. If brief exposures to inescapable shock produce a nonopioid analgesia,

whereas a more extended exposure results in an opioid form, animals exposed to a long series of inescapable shocks should display nonopioid and opioid forms of SIA sequentially.

Grau *et al.* [14] repeatedly tested animals for analgesia after 20, 40, 60 and 80 inescapable 5 sec shocks without removing the subjects from the shock apparatus. They found that subjects displayed an early naltrexone-insensitive form of analgesia after only 20 shocks. However, after 60 and 80 shocks, the analgesia observed was reversed by the opiate antagonist. Thus, there were both early and late analgesic peaks, with only the late peak being sensitive to opiate antagonists.

There are a number of potential difficulties with this interpretation of the data, reported in Grau *et al.* [14]. First, they based their conclusion concerning the opioid/nonopioid mediation of the early and late analgesic peaks on only one dose of naltrexone (14 mg/kg). Thus it is not known whether the early "nonopioid" analgesia is generally insensitive to naltrexone or whether its reversal simply requires a different dose than does the late peak. Experiment 1 addresses this issue. Second, all subjects in the experiments of Grau *et al.* received inescapable shock. There were no groups which received escapable shock. It is possible that the naltrexone sensitive analgesia measured by Grau *et al.* [14] immediately after 80 shocks is not specific to inescapable shock [20]. Thus, the general question of whether the occurrence of opioid mediated analgesia is influenced by the learning of uncontrollability remains unanswered. Experiment 2 addresses this problem.

As noted earlier, 80 inescapable shocks produce a long-term analgesic reaction upon brief reexposure to shock 24 hr later [15]. Grau *et al.* [14] found that subjects given this long exposure to inescapable shock were also hyperreactive to the analgesic effects of morphine 24 hr later. They suggested that the initial activation of an endogenous opiate system might result in some post-release sensitization of the opiate system, thereby enhancing morphine produced analgesia. They went on to suggest that this sensitization may also account for the long-term analgesic reaction upon reexposure to shock. That is, the brief reexposure to shock may result in a release of endogenous opiates which is not sufficient to result in analgesia in stress-naive subjects. However, since the opiate responsive system is sensitized in previously inescapably shocked subjects, the resulting analgesia is observed.

If hyperractivity to morphine and long-term analgesia after brief reexposure to shock are caused by a similar sensitization process, then both should occur only after an extended series of inescapable shocks. This is exactly what Grau, *et al.* [14] observed; 80 shocks produced hyperreactivity to morphine, whereas 40 did not. It has been shown that escapable shock does not lead to the long-term form of analgesia [15]. If hyperreactivity to morphine is a result of a similar process, then it, too, should be influenced by the controllability of the initial shock pretreatment. Experiment 3 tests this hypothesis.

EXPERIMENT 1

The purpose of this experiment was to examine the generality of the naltrexone sensitivity/insensitivity dichotomy between the early and late analgesic reactions produced by inescapable shock. Rats were given doses of naltrexone ranging from 1.75 to 28.0 mg/kg before receiving a series of 80 inescapable shocks in an apparatus where tail-flick to radiant heat could be tested without removing the subject from the shock apparatus. Tail-flick responding was measured after 0, 20, 40, 60, and 80 shocks. Grau *et al.* [14] injected naltrexone (14 mg/kg) 20 min before the inescapable shock session and found it to block the second analgesic peak, but to have no effect on the first peak. However, 40 min elapsed between injection and testing for the first peak, whereas 80–100 min elapsed before testing for the second peak. It was possible that the drug had been in the system an insufficient period of time to exert its effect at the time of the initial peak. Thus, in a second experiment naltrexone was administered 80 min before the session (100 min before testing the first peak), and again, the late but not the early peak was blocked. Here we chose to inject naltrexone 80 min before the session. Thus any naltrexone insensitivity of the first analgesic peak cannot be attributed to the interval of time between injection and testing. This is because a 100 min injection to testing interval was adequate to block the second peak in Grau, *et al.* [14].

METHOD

Subjects

The subjects were 96 male albino rats obtained from the Holtzman Company (Madison, WI). The animals were 90–120 days old at the start of the experiment. They were maintained on a 12 hr light/dark cycle and had food and water continuously available in the home cages.

Apparatus

Inescapable shock or restraint occurred in Plexiglas restraining tubes which were 17.5 cm in length and 7.0 cm in diameter. The rat's tail extended from the rear of the tube and could be taped at the base to a Plexiglas rod 4.0 cm in length. The front end of each tube was closed off and 4 air holes were drilled on either side of the tube. The design of this tube allowed for analgesia testing without removing the animal from the apparatus. Unscrambled shocks (1.0 mA) were delivered by shock sources (modeled after the Grason-Stadler Model 700 shock source) through electrodes taped to the rat's tail and augmented with electrode paste. The electrodes were constructed from fuse clips modified to deliver shock to the tip of the rat's tail.

Analgesia testing was conducted using a tail-flick apparatus consisting of a 43.0×17.7×8.0 cm (L×W×H) metal box which supported a 7.4×3.0 cm (l×w) aluminum plate. A shallow groove was cut in this plate and the rat's tail was placed in this slot during a trial. A General Electric 150-W projector spotlight was mounted above the slot. A condenser lens located between the light source and the slot focused the light on the rat's tail. A lateral deflection of the tail of at least 5 mm activated a photocell receiver and automatically terminated the trial.

Procedure

The rats were randomly divided into 12 groups (n=8). Subjects were given a subcutaneous injection of either 1.75, 3.5, 7.0, 14.0, 28.0, mg/kg naltrexone hydrochloride or its vehicle, saline. Eighty min later all subjects were placed in restraining tubes and a single baseline tail-flick test was given approximately 2 min later. The base of the tail was then taped down and electrodes were fixed near the tip of the tail. Half of the subjects received 20 inescapable unsignaled

1.0 mA 5 sec shocks with a mean intertrial interval of 60 sec (range 5–200 sec). The other half received an equivalent period of restraint. Immediately after the final shock the electrodes were removed and the tail was untaped. A single tail-flick test trial was administered without removing the rat from the restraining tube. The electrodes were then reattached and this procedure of 20 shocks or only restraint, followed by tail-flick testing, was repeated 3 more times (a total of 80 shocks). Care was taken to avoid shocking and testing on the same portion of the tail. In order to prevent tissue damage, each tail-flick test was terminated if the subject did not respond in 10 sec and each test was on a different portion on the tail.

RESULTS AND DISCUSSION

Figure 1 shows the mean tail-flick latencies for all groups across the 80 shock test session. As can be seen, only those animals receiving inescapable shock showed changes in pain reactivity. Moreover, the increased tail-flick latencies in the inescapably shocked saline controls appear to show the early and later peaks reported by Grau, *et al.* [14]. An overall analysis of variance revealed a significant effect of shock, $F(1,84)=83.60$, $p<0.001$, a significant trials effect, $F(4,336)=13.03$, $p<0.001$, and a significant shock × trials interaction, $F(4,336)=15.84$, $p<0.001$. Further, inspection of Figure 1 reveals that the analgesia after 20 trials of shock is insensitive to naltrexone blockade at any dose. However, after 60 and 80 trials the analgesia observed appears to be attenuated by naltrexone in a dose dependent fashion. Thus, we performed separate 2-way analyses of variance after 20 trials of shock, our proposed nonopioid analgesia, and on the pooled data after 60 and 80 trials of shock, our proposed opioid mediated analgesia. Our main concern was to determine if any dose of naltrexone had an effect on the early nonopioid analgesia.

These analyses confirmed the above conclusions. Following 20 trials of shock there was a significant effect of shock, $F(1,84)=97.5$, $p<0.001$, with no significant effect of dose of naltrexone, $F(5,84)<1.0$, or shock by dose interaction, $F(5,84)<1.0$. Post hoc Newman-Keuls comparisons ($p<0.05$) indicated that subjects in all the shock groups differed from all the restrained groups. No other comparisons were significant. At 60 and 80 shocks there was also a significant effect of shock, $F(1,180)=74.23$, $p<0.001$, and no significant effect of drug dose, $F(5,180)=14.7$, $p>0.1$, however the shock by dose interaction approached significant, $F(5,180)=2.16$, $p=0.06$. Post hoc Newman-Keuls comparisons ($p<0.05$) indicated that shocked subjects receiving 14 or 28 mg/kg naltrexone differed significantly from the inescapably shocked saline control group, indicating a naltrexone blockade. All shocked groups with the exception of the group receiving 28 mg/kg naltrexone differed from their appropriate restrained control group.

These results indicate that the early analgesia which occurs after 20 trials of inescapable shock, is indeed insensitive to naltrexone blockade. This lack of effect of the opiate antagonist was found over a wide range of doses. The analgesia after 60 and 80 trials, however, does appear to be attenuated in a dose dependent fashion. Thus, if reversal by naltrexone is used as a criterion, these data support the conclusions of Grau *et al.* [14]. That is, only after extended exposure to inescapable shock does analgesia appear to be, at least in part, mediated by opiate systems.

It may be noted that in this and the other experiments of this report we both shock and test for analgesia on the tail. There is the possibility that the changes in analgesia observed are local to the tail. However, we have previously tested this possibility by testing for analgesia using a hot plate procedure [14,15]. Regardless of test used the pattern of results remained the same.

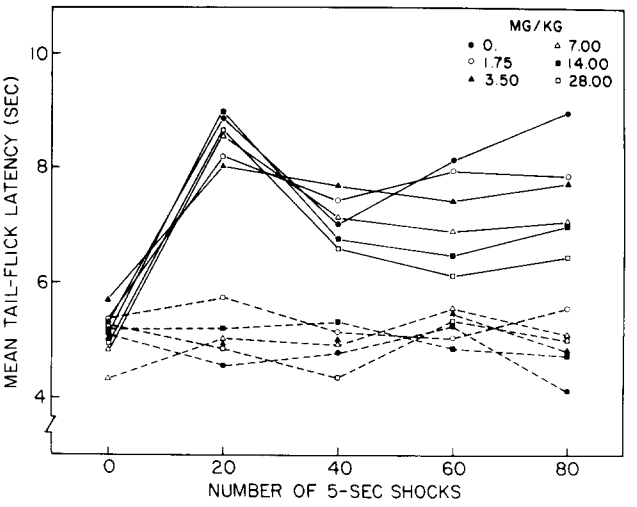

FIG. 1. Mean tail-flick latencies during inescapable shock (solid lines) or restraint (broken lines) for subjects given various doses of naltrexone (see key).

EXPERIMENT 2

Although Experiment 1 confirms the fact that naltrexone sensitive analgesia occurs only after extended exposure to the stressor, the importance of the controllability/uncontrollability dimension remains unaddressed. Gray *et al.* [14] proposed that it was the learning of uncontrollability that leads to the activation of opiate systems. However, all subjects in their studies and in Experiment 1 received inescapable shock. It is possible that the opioid/nonopioid differentiation seen in these studies is simply due to extended exposure to shock *per se*.

As already noted, escapable shock only produces a small antinociceptive response when pain sensitivity/reactivity is measured 30 min after the session and does not lead to any detectable analgesic reaction 24 hr later upon reexposure to shock. However, when pain sensitivity/reactivity is assessed immediately after the subject is removed from the apparatus subsequent to the 80 shock session, escapable shock produces an analgesic reaction which appears to be as strong as that produced by inescapable shock [20]. Since the time of testing beyond the termination of the 80th shock in this experiment differed from that in Grau *et al.* [14] and Experiment 1 here, by only the time taken to remove the subject from the shock apparatus, it is possible that the opiate analgesia at 80 shocks is not specific to uncontrollable shock. It is not possible to manipulate the controllability of shock in the apparatus used in Experiment 1. However, even if 80 escapable shocks produce an analgesic reaction as large as that produced by inescapable shock, it is possible that the two shock procedures decrease pain sensitivity/reactivity by different mechanisms. The learning of uncontrollability

might still be entirely or partly responsible for opiate system activation, thus yielding an antinociceptive reaction immediately after inescapable shock that is more dependent on opiate systems than is the antinociceptive reaction after escapable shock. This line of argument suggests that even though both escapable and inescapable shock might produce a potent analgesia immediately after 80 shocks, the antinociceptive reaction of the inescapably shocked subjects might be more sensitive to blockade by opiate antagonists. Experiment 2 tests this hypothesis. Subjects were given naltrexone or saline prior to receiving 80 trials of escapable shock, yoked-inescapable shock, or restraint. Analgesia was tested immediately after the session.

METHOD

Subjects

The subjects were 90 rats of the same age, sex, and strain as in Experiment 1. Housing conditions were also identical.

Apparatus

Shock or restraint occurred in one of three wheel-turn boxes, 15.5×12.0×17.0 cm (l×w×h), modeled after those used by Weiss, Stone and Harrell [29]. The front and side walls were made of clear Plexiglas; the rear wall and floor were made of Masonite. A grooved Plexiglas wheel extended 1.7 cm into the front of the chamber through a hole 8.0 cm from the floor of the box. The wheel required about 0.5 N of force to turn. The rat's tail extended through a slot in the rear wall and was taped to a Plexiglas rod. Electrodes were attached to the rat's tail and augmented with electrode paste. The shock sources were modeled after the Grason-Stadler Model 700. Pain sensitivity was measured with the tail-flick apparatus described in Experiment 1.

Procedure

The subjects were randomly divided into 9 groups (n=10). Subjects were injected (SC) with 7.0 or 14.0 mg/kg naltrexone hydrochloride, or its vehicle, saline. Twenty min after injection the subjects were placed in the wheel-turn boxes and given one of three treatments. In the first condition (escape), subjects were given escapable shock which consisted of 80 unsignalled shock trials with a variable mean intertrial of 60 sec (range 30–120 sec). Shock could be terminated by turning the wheel one-half of a complete rotation after the first 0.8 sec of shock. Responses within 0.8 sec of shock onset had no consequence. Shock terminated automatically if the subject had not responded after 30 sec. Shock intensity was initially 0.8 mA and was incremented to 1.0 mA after 20 shocks, 1.3 mA after 40 shocks and 1.6 mA after 60 shocks. This was done in order to maintain responding.

Subjects in the second condition (yoked) were each paired with a member of the escape group. These subjects received the same intensity and duration of shocks as did their respective partners. Wheel turning had no effect on shock termination in this group, and shock terminated whenever the escape subject responded.

The third group of rats (restrained) were merely restrained in the wheel-turn boxes for an equivalent period of time.

Immediately following escapable shock, yoked-inescapable shock, or restraint, each subject was removed from the wheel-turn box and given 3 tail-flick trials separated by approximately 2 min. On a test trial the experimenter, unaware of group membership, held the rat in his hand. The rat's tail was placed in the groove and the lamp was turned on. In this experiment the heat of the lamp was adjusted to be less severe than in Experiment 1 and a cutoff of 21 sec was used. All tests were completed within 6–10 min after the final shock.

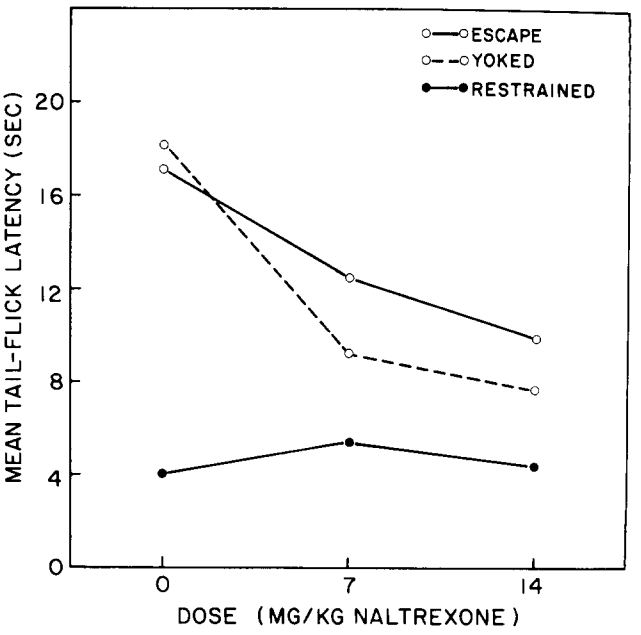

FIG. 2. Mean tail-flick latencies after escapable shock, yoked-inescapable shock or restraint for subjects given different doses of naltrexone.

RESULTS AND DISCUSSION

All subjects in the escape group learned the wheel-turn response. Latency to respond was shorter during the last 10 trials than during the first 10 for each subject. Figure 2 presents the mean tail-flick latency immediately after receiving escapable shock, yoked-inescapable shock, or restraint, for subjects given 0, 7 or 14 mg/kg naltrexone. As can be seen both escape and yoked groups were analgesic relative to restrained controls. However, the analgesic reaction of subjects in the yoked group was more affected by naltrexone than was that of the escape group. Analysis of variance revealed a significant effect of dose, $F(2,81)=24.96$, <0.001, shock treatment, $F(2,81)=49.37$, $p<0.001$, and treatment × dose interaction, $F(4,81)=6.18$, $p<0.001$. Planned orthogonal comparisons ($p<0.05$) revealed that the subjects in the escape group given 7 and 14 mg/kg naltrexone differed from subjects in the yoked group receiving the same doses, $F=5.48$, $p<0.05$. Post hoc Newman-Keuls comparisons ($p<0.05$) revealed that these groups also differed from their restrained controls and from their shocked, saline controls.

These data indicate that subjects given either escapable or inescapable shock are strongly analgesic immediately following the shock session. Although naltrexone significantly reduces analgesia in both of these groups, the analgesia of inescapably shocked subjects was more readily reduced by the opiate antagonist. This supports the conclusions of Grau *et al.* [14], Jackson, *et al.* [15], and Maier, *et al.* [20] that the

controllability/uncontrollability of a stressor is an important determinant of the type of SIA which occurs.

EXPERIMENT 3

Experiments 1 and 2 have dealt with the effects of extent and control of shock on the form of analgesia observed immediately following the stress session. However, these shock conditions are also known to have long-term effects on antinociceptive systems. As noted, brief exposure to shock 24 hrs after inescapable shock results in analgesia [15] which is reversed by opiate antagonists [19] and cross tolerant with morphine [13]. Importantly, this analgesia is not observed if the subject has experienced escapable shock [15]. Moreover, in an analogous procedure, Grau *et al.* [14] reported that subjects given inescapable shock were hyperreactive to the analgesic effects of morphine 24 hrs after inescapable shock exposure. This enhanced analgesic potency of morphine was observed only after extended exposure to inescapable shock. Thus, they suggested that the initial activation of an endogenous opiate system (which also occurs only after extended exposure to shock) resulted in a post-release sensitization of this system, and that this sensitization might account for the long-term analgesia observed after brief reexposure to shock. They argued that the animal's learning that it had no control over shock led to this initial activation and consequent sensitization of the opiate system.

Experiment 2 of this report indicated that subjects given inescapable shock did display analgesia which relied on an opiate system to a greater extend that did the analgesia of subjects given escapable shock, thus supporting the argument that inescapable shock leads to a greater activation of an opiate system. If this activation leads to sensitization, then animals given inescapable shock should show a greater analgesic response to morphine 24 hr post-stress than those given escapable shock. The present experiment tests this hypothesis. Subjects were given either escapable shock, inescapable shock, or restraint; then, 24 hr later they were tested for their analgesic reaction to a low dose of morphine. No saline injected controls were employed in the present study since previous research has shown that there is no evidence of residual analgesia 24 hr after either inescapable or escapable shock [14,15].

METHOD

Subjects

The subjects were 24 rats of the same age, sex, and strain as used in the previous experiments. Housing conditions were also identical.

Apparatus

The apparatus was the same as described in Experiment 2.

Procedure

The subjects were randomly divided into 3 groups (n=8). Each subject was placed into a wheel-turn box and given either escapable shock, yoked, inescapable shock or merely restraint as in Experiment 2. Twenty-four hrs after shock or restraint all subjects were given a subcutaneous injection of morphine (1 mg/kg). Thirty min after injection the subjects were given 3 tail-flick tests using the procedure described in Experiment 2. A 15 sec cutoff was employed.

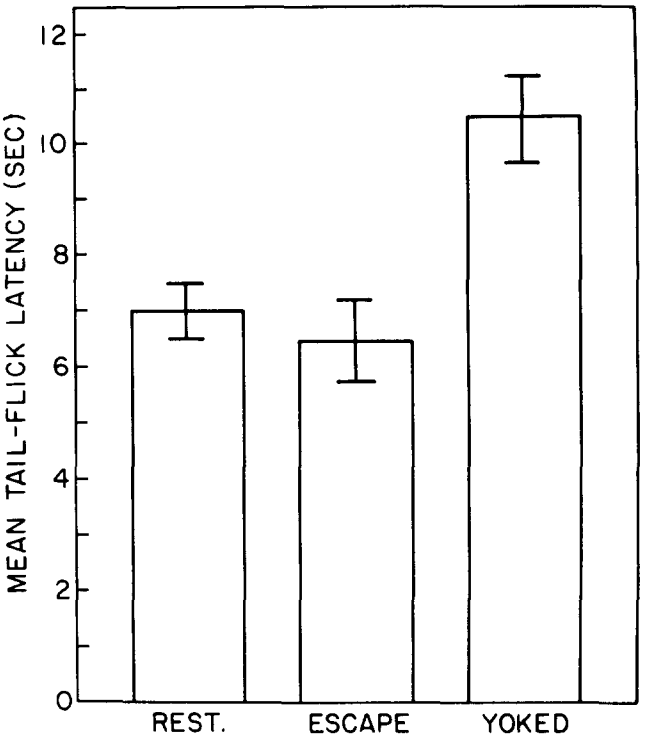

FIG. 3. Mean tail-flick latencies for subjects given an injection of morphine 24 hr after escapable shock, yoked-inescapable shock or restraint.

RESULTS AND DISCUSSION

All subjects in the escape group learned the wheel-turn response. Latency to respond was shorter during the last 10 trials than during the first 10 for each subject. Figure 3 depicts the mean tail-flick latencies for each group 30 min after receiving the 1 mg/kg injection of morphine. As is apparent, the subjects receiving inescapable shock 24 hr before the injection of morphine were substantially more analgesic than subjects receiving either escapable shock or restraint. These observations were statistically confirmed. A one-way analysis of variance revealed a significant groups effect, $F(2,21)=10.11$, $p<0.001$, and subsequent Newman-Keuls comparisons confirmed that the yoked group differed significantly from both the escape and restrained groups ($p<0.01$) which did not differ from each other.

These results indicate that only inescapable shock leads to a hyperreactivity to the analgesic effects of morphine. Animals given an equivalent amount of escapable shock were no more responsive to morphine than were restrained controls. This supports the conclusion of Grau, *et al.* [14] that the controllability of the stressor is a critical factor influencing opioid processes.

GENERAL DISCUSSION

The results of the experiments reported are clear. Exposure to a series of 80 inescapable shocks produced two analgesic peaks, one after 20 shocks (the first point assessed), and one after 60 or 80 shocks. The first peak was totally unaffected by any dose of naltrexone in the wide range explored, while the second peak was reduced in a dose dependent fashion. This supports the contention that exposure

to a small number of shocks produces nonopiate mediated analgesia, whereas an extended series of inescapable shock is required to activate opioid mechanisms of analgesia. However, it is not clear whether naltrexone completely blocked the second peak. Only a very high dose of naltrexone (28 mg/kg) resulted in a statistically complete block of analgesia after 60 and 80 shocks. Only where was there no longer a reliable difference from nonshocked controls. However, there was still a full second difference between the tail-flick latencies of shocked and restrained subjects given this dose and it is possible that high doses may result in effects not specific to opiate systems. Thus the "purity" of opioid mediation of analgesia at 60 and 80 shocks seems, at best, ambiguous. Maier *et al.* [19] administered naltrexone before 80 inescapable shocks of identical parameters to those used in Experiment 1. However, they tested tail-flick responding 30 min after the inescapable shock (Experiment 5). Both 7.0 and 14.0 mg/kg completely blocked the analgesia observed. In contrast, naltrexone was injected only 20 min before the session in Experiment 2 here, and still produced only a partial block when analgesia was tested 1–2 min after shock. This suggests that there may be a residual analgesia after an extended series of shocks not resulting from an opiate process. This nonopioid process appears to be quite transient. It is present immediately after the 80th shock (Experiment 1) and 1–2 min after the termination of the session (Experiment 2). However, it is no longer present 30 min after the session (19, Experiment 5).

The existence of a very transitory nonopiate analgesia following a stress session may help to explain a number of ambiguities in the literature. Even when shock conditions leading to an opioid form of analgesia have been used, the impact of opiate manipulations have frequently not been observed immediately after shock. For example, Lewis *et al.* [17] examined cross tolerance between morphine and a shock procedure known to produce naloxone reversible analgesia. Rats were made morphine tolerant or were given only saline as a control, and then received inescapable shocks. Analgesia testing began immediately after shock and was repeated at one min intervals. The morphine tolerant and control subjects were equally analgesic immediately after shock. It was not until 5 min post-shock that the groups diverged, with the morphine subjects showing attenuated analgesia (cross tolerance). Similarly, the antagonistic effects of naloxone are sometimes not observed until several minutes following the end of the shock session [11], and even where present, grow over the first few minutes [16]. Finally, the effects of prior dorsolateral column lesions grow over the first few minutes post-shock [28]. A brief nonopioid analgesia might be expected to obscure or mask the effects of opiate manipulations. The effects of opiate manipulations should be most clearly revealed when this other antinociceptive reaction has dissipated. Thus the nonopioid analgesia isolated here may help to explain why the effects of opiate manipulation frequently increase with the time since the end of stress.

Although the implications of the data for the role of the number of shocks in activating opiate systems is clear, the conclusions that can be drawn with regard to controllability are less clear. Both escapable and inescapable shock produced an equally strong analgesic reaction when measured shortly after the shock session. Further, the simple argument that the antinociceptive reaction seen after escapable shock reflects only a nonopioid process is not tenable since naltrexone did have an observable effect on the analgesia in this group. However, naltrexone did exert a reliably greater effect on the decrease in pain sensitivity/reactivity observed in the inescapable than the escapable groups. Thus it would appear that the balance between opioid and nonopioid analgesic processes differ depending on the controllability of the stressor, with opioid processes being a greater contributor in the uncontrollable stress case.

Grau *et al.* [14] argued that the long-term analgesia produced by shock reexposure 24 hr after the initial shock session occurs through purely opioid mechanisms. This was argued because the analgesia was completely reversed by opiate antagonists [19] and cross tolerant with morphine [13], and because analgesia could not be reinstated 24 hr after 20 shocks. As shown above, 20 shocks produce only a nonopioid analgesia. Grau *et al.* [14] argued that the activation of opiate systems by extended shock sensitized some post-release process. They found that a long exposure to inescapable shock led to a hyperreactivity to the analgesic effects of morphine 24 hrs later. Experiment 3 indicates that the controllability of the shock is an important determinant of this subsequent hyperreactivity. Although escapable shock does result in analgesia immediately after the stress session which is, in part, naltrexone sensitive (Experiment 2), escapably shocked subjects are not hyperreactive to morphine 24 hrs later (Experiment 3). Thus, although escapable shock does activate opiate systems, the system is not sensitized as assessed by reactivity to morphine. Given the data of Experiment 2, it may be that escapable shock does not result in a sufficient degree of opioid activation to result in sensitization, or the balance between opioid and nonopioid processes may be important for this sensitization to occur.

Other investigators [12, 17, 27] have also observed enhanced analgesic effects of narcotics after experience with painful or stressful events. Colpaert, Carlos, Niemegeers, Janssen and Maroli [12] applied alligator clips to the hindpaws of rats, twice a day for 4 days. On the fifth day these subjects were hyperreactive to the analgesic effects of fentanyl. Sherman, Lewis, deWetter and Liebeskind [27] found that rats were hyperreactive to the analgesic effects of morphine when tested in an environment which had previously been paired with shock. They suggested that conditioned fear may contribute to this phenomena. That is, the expectation of pain, not pain per se was was responsible for this enhancement effect. It should be noted that in these experiments the nociceptive events were always uncontrollable. In Experiment 3, here, we also found an enhanced reaction to morphine after uncontrollable shock. However, this hyperreactivity did not occur when the shock was controllable. There was little opportunity for conditioned effects in this experiment. Animals were shocked in a novel environment but were injected with morphine in the colony room. In addition, unlike the previous enhancement studies, subjects were given only one session of stress. The results clearly indicate that uncontrollable shock, not shock per se is necessary for the hyperreactivity to morphine. Thus, the uncontrollability of the nociceptive stimulation in the aforementioned studies may be a critical factor for the observation of enhanced narcotic analgesia. This effect may be due to a greater activation of opiate systems during uncontrollable stress than during escapable stress (Experiment 2). This initial activation may act to sensitize opioid systems to subsequent activation.

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