Immunization of Opioid Analgesia: Effects of Prior Escapable Shock on Subsequent Shock-Induced and Morphine-Induced Antinociception

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In Experiment 1, it was shown that experience with escapable foot shock 4 hr prior to a session of 80 inescapable tail shocks prevented the occurrence of an analgesic response normally observed immediately following the tail shock. It has been suggested by J. W. Grau, R. L. Hyson, S. F. Maier, J. Madden, and J. D. Barchas (Science, 1981, 213, 1409–1411) that the analgesia that occurs following this number of inescapable tail shocks is mediated by endogenous opioid systems. To further explore the influence of escapable shock on opiate-mediated analgesia, Experiment 2 examined the effects of prior escapable shock on the long-term analgesia reaction that occurs upon brief exposure to shock 20 hr after morphine administration. Rats were given escapable shock, inescapable shock, or no shock 4 hr prior to a morphine injection. Twenty hours following the injection, all subjects received 5 brief foot shocks and were then immediately given tail-flick analgesia tests. Subjects which received inescapable shock or no shock prior to the morphine injection displayed a significant analgesic response. However, subjects which received escapable shock prior to morphine were not analgesic following brief exposure to shock. Thus, escapable shock seems to directly influence the activation of opioid analgesia systems.

The effects of stressful stimulation on subsequent nociceptive responding has recently received considerable attention. A number of studies have clearly shown that exposure to stressors such as foot shock (Akil, Madden, Patrick, & Barchas, 1976; Hayes, Bennett, Newlon, & Mayer, 1978), tail shock (Maier, Drugan, & Grau, 1982; Grau, Hyson, Maier, Madden, & Barchas, 1981), cold-water swims (Bodnar, Kelly, & Glusman, 1978), and severe immobilization (Amir & Amit, 1978) all produce decreased

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responsiveness to subsequent painful stimuli. This decreased reactivity to pain following stress occurs in humans as well as animals (Willer, Dehen, & Cambier, 1981) and is generally termed stress-induced analgesia.

Many recent studies have attempted to assess the possible role of endogenous opioid systems in the production of stress-induced analgesia, but the results of these studies have been equivocal. Some have demonstrated that stress-induced analgesia can be completely blocked by opiate antagonists such as naloxone (Amir & Amit, 1978) and is completely cross-tolerant with morphine (Drugan, Grau, Maier, Madden, & Barchas, 1981). However, other studies have found stress-induced analgesia to be insensitive to opiate antagonists and to produce no cross-tolerance with morphine (Bodnar, Kelly, Steiner, & Glusman, 1978; Chance & Rosecrans, 1980). This inconsistency of results suggests the existence of both opioid and nonopioid forms of stress-induced analgesia.

Lewis, Cannon, and Liebeskind (1980) were able to produce both opioid and nonopioid forms of analgesia in rats by exposing them to foot shock. Three minutes of continuous foot shock produced an analgesia insensitive to naloxone, while the analgesia observed following 20 to 30 min of intermittent foot shock was completely reversed by naloxone and cross-tolerant with morphine. Similarly, Grau et al. (1981) recently demonstrated the occurrence of both nonopioid and opioid analgesias during a session of inescapable tail shock. In this study, rats’ tail-flick latencies to radiant heat were measured following 0, 20, 40, 60, and 80 shocks. It was found that an analgesic reaction occurred following 20 shocks, dissipated after 40 shocks, and emerged again after 60 and 80 shocks. Administration of the opiate antagonist naltrexone prior to the session of tail shock had no effect on the early occurring analgesia observed after 20 shocks, while the later occurring analgesia that developed after 60–80 shocks was blocked by this treatment. This result suggests that the early occurring analgesic response is produced through a nonopioid system, while the later occurring analgesia is mediated in some fashion by an opioid mechanism.

A factor that seems critical to the development of the later occurring opiate form of analgesia induced by tail shock is the escapability/inescapability of the shock. A session of 80 inescapable tail shocks produces a subsequent analgesia that is antagonized by naltrexone much more completely than the analgesia induced by an equivalent amount of escapable tail shock (Hyson, Ashcraft, Drugan, Grau, & Maier, 1982). In addition, only inescapable tail shock produces an analgesia which is reinstatable 24 hr later by brief reexposure to shock (Jackson, Maier, & Coon, 1979). This long-term analgesic reaction is completely reversible by opiate antagonists (Maier, Davies, Grau, Jackson, Morrison, Moye, Madden, & Barchas, 1980), and is cross-tolerant with morphine (Drugan et al., 1981). These results suggest that the inescapability of the shock, rather than
shock *per se*, is a critical factor in the production of an opioid form of stress-induced analgesia.

Maier *et al*. (1982) have proposed that the opioid analgesia that occurs following a large number (60–80) of inescapable shocks is a consequence of the subjects’ learning that the stressor is uncontrollable. If this learning of uncontrollability during a session of inescapable shock could be interfered with, the analgesia normally observed after a large number of shocks might not occur. Previously, we have demonstrated that a session of escapable shock prior to a session of inescapable shock (in effect, an “immunization” treatment) prevents the occurrence of the long-term reinstatable analgesia normally observed following inescapable shock (Moye, Coon, Grau, & Maier, 1981). That is, subjects exposed to reinstating shock 24 hr following inescapable shock did not become analgesic if they had first experienced escapable shock. Experiment 1 of the present study examines the effect of prior experience with escapable shock on the subsequent pattern of analgesia observed *during* a session of 80 inescapable shocks. Perhaps learning that shock is controllable will later interfere with the learning of uncontrollability during the subsequent session of inescapable shock. If learning that shock is uncontrollable is a necessary condition for the production of the opioid analgesia observed following 80 inescapable shocks, interference with that learning may prevent the analgesia from occurring.

**EXPERIMENT 1**

This experiment investigated the effect of experience with escapable shock on the pattern of analgesic responses elicited during a subsequent session of inescapable shock. In the first phase, one group of rats was given shock escape/avoidance training in a two-way shuttlebox. A yoked group of rats received an equivalent amount of inescapable shock in a shuttlebox. A third group was merely placed in a shuttlebox for a similar period of time with no shock. Four hours later, all subjects were given a session of 80 inescapable tail shocks in restraining tubes. Tail-flick pain reactivity tests were given following 0, 5, 20, 40, and 80 inescapable shocks.

**Method**

**Subjects.** Thirty male, albino rats (90 to 120 days old) of Holtzman descent, raised at the University of Colorado and weighing 300–400 g at the beginning of testing, served as subjects. They were maintained on a 12-hr light/dark cycle and had food and water continuously available in the home cages. Experimental sessions began approximately 3 hr after lights on.

**Apparatus.** Escapable foot shock, yoked inescapable foot shock, or no shock was carried out in four identical two-way shuttleboxes. The
shuttleboxes measured 34.9 × 20.5 × 19.5 cm (L × W × H). Each chamber was divided into two equal-sized compartments by a metal wall which spanned width of the box from floor to ceiling. A rectangular opening 5.2 cm high and 5.5 cm wide was cut in the bottom of the metal wall to allow rats to cross back and forth between compartments. The floor consisted of stainless steel grids 0.35 cm in diameter, and spaced 1 cm apart. Scrambled 0.6-mA shocks were delivered across the grids by four separate constant-current shock sources. Subsequent inescapable tail shock occurred in four 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 cm in length. The front of each tube was closed off and eight air holes were drilled in the sides of each tube near the location of the rat’s head. The design of this tube allowed for tail-flick analgesia testing without removing the subject from the apparatus. Unscrambled 1.0-mA electric shocks were delivered by four separate constant-current shock sources through electrodes taped to the rat’s tail and augmented with electrode paste. The electrodes were constructed out of fuse clips modified to deliver shock to the tip of the rat’s tail.

Analgesia testing was conducted using a tail-flick device, which consisted 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 slot was cut in this plate, and the rat’s tail was placed in this slot during a trial. A photocell receiver was mounted in the bottom of the slot. A General Electric 150-W spotlight was mounted above the slot which held the rat’s tail. A condenser lens was located 6.5 cm above the slot, and served to focus the light on the rat’s tail. A lateral deflection of the tail of at least 5 mm activated the photocell receiver and automatically terminated the trial. The heat was adjusted so that naive control rats showed tail-flick latencies in the range 4–6 sec.

Procedure. The subjects were randomly assigned to one of three groups (n = 10/group). Subjects in Group ES were given 48 trials of shuttlebox escape/avoidance training. Trials were presented on a variable time 60-sec schedule (range 5–150 sec). The beginning of each trial was signaled by a 1000-Hz tone which raised the background noise level from approximately 70 to 75 dB (re 0.0002 dyn/cm²). If no response occurred within 5 sec of tone onset, a 0.6-mA shock was delivered, and terminated whenever the appropriate response occurred. If no response occurred within 35 sec of tone onset, the trial was automatically terminated. During the first 24 trials of escape/avoidance training, one crossing (FR-1) of the shuttlebox after tone onset either prevented or terminated the shock. During the last 24 trials, the subject was required to cross the shuttlebox twice (FR-2) in order to avoid or escape shock. Each subject in Group YS was randomly assigned a partner in Group ES. During escape/avoidance
training, subjects from Group YS were placed in the shuttlebox and received amounts of uncontrollable shock equal to those their partners in Group ES received. Each member of an ES–YS pair received tone and shock at the same time, and the trial terminated whenever the ES subject responded appropriately. Subjects in Group RS were simply placed in a shuttlebox for periods of time equal to subjects in the ES and YS groups.

Four hours following the end of the shuttlebox session, subjects in all groups were placed in the restraining tubes. Each subject was then given a baseline analgesia tail-flick test (time point zero). Following the baseline analgesia test, the shocking system was taped to the rat’s tail, and the session of inescapable tail shock commenced. The session consisted of 80, 1-mA shocks, each of 5-sec duration. The shocks were presented on a variable time 60-sec schedule (range 5–200 sec). During this session, the subjects were tested for pain responsiveness using the tail-flick test after 5, 20, 40, or 80 shocks had occurred. Care was taken to avoid shocking and/or testing on the same spot on the rat’s tail. A tail-flick test trial was terminated if a response did not occur within 10 sec in order to prevent tissue damage to the tail.

A .05 rejection region was adopted for all statistical analyses.

Results and Discussion

All subjects in Group ES responded on each trial during the 24 FR-1 and 24 FR-2 shuttlebox escape trials. The mean latency to escape during the 48 total trials was 9.1 sec. The mean tail-flick latencies recorded following 0 (baseline), 5, 20, 40, and 80 inescapable tail shocks are presented in Fig. 1.

Analysis of variance revealed a significant trials effect \(F(4, 108) = 14.12\), and a significant Group × Trials interaction \(F(8, 108) = 2.55\). Subsequent Duncan’s post hoc individual comparisons (\(\alpha = .05\)) indicated that the three groups did not differ from one another when tested immediately prior to the session of inescapable tail shock (zero shocks point). This shows that the prior experience with escapable or inescapable foot shock 4 hr earlier had no effect on baseline responding. Further comparisons were made between each group’s own baseline tail-flick latency and the subsequent latencies recorded after 5, 20, 40, or 80 tail shocks, again using Duncan’s individual comparisons (\(\alpha = .05\)). After 5 shocks, Groups ES and YS displayed tail-flick latencies significantly longer than baseline latencies. Group RS displayed a nonsignificant increase in tail-flick latency after 5 shocks. The latency of Group YS was also reliably longer than that of Group RS after 5 shocks. Group ES did not differ from either Group YS or Group RS at this point. After 20 shocks, all three groups produced tail-flick latencies significantly longer than baseline latencies and none of the groups differed reliably from one
another. Thus following 5 or 20 shocks, all groups displayed an early occurring analgesic reaction. Subjects receiving foot shock (escapeable or inescapable) 4 hr prior to the session of tail shock produced significantly elevated tail-flick latencies after only 5 shocks, while Group RS did not display a significantly elevated latency until after 20 shocks. Furthermore, the group given inescapable foot shock (Group YS) produced a latency significantly longer than Group RS following 5 tail shocks. These comparisons suggest that exposure to foot shock (escapeable or inescapable) may have sensitized the system responsible for producing the early occurring nonopioid analgesia, in that fewer tail shocks were necessary to produce significant increases in tail-flick latency. Prior inescapable foot shock (Group YS) seems to have produced a stronger sensitization effect than escapeable foot shock (Group ES) since only Group YS produced a latency reliably longer than Group RS after 5 shocks. However, as already noted, Group YS latencies were not significantly longer than those for Group ES, although the 10-sec cutoff latency employed could have resulted in a “ceiling” effect in Group YS which would prevent the detection of a significant difference between groups YS and ES. Thus any conclusions regarding an ES–YS difference after 5 shocks should be regarded as tentative at best. After 40 shocks, all three groups displayed decreased latencies to tail-flick as compared to the latencies recorded following 20 shocks. In fact, none of the groups differed significantly from baseline responsiveness.

The data of primary interest are the tail-flick latencies recorded following 80 shocks. As can be seen in Fig. 1, Groups YS and RS displayed a
second increase in tail-flick latency. The latencies of both groups were significantly elevated above their baseline latencies, demonstrating a second analgesic response following 80 shocks. Furthermore, Groups YS and RS did not differ from one another after 80 shocks. However, the mean tail-flick latency for Group ES following 80 shocks was nearly identical to the baseline latency recorded prior to the inescapable shocks session and significantly shorter than those of Groups YS and RS, indicating the absence of a second analgesic response. Thus the experience of escapable footshock 4 hr prior to a session of inescapable tail shock prevented the occurrence of the second analgesic reaction normally observed following 80 shocks. An equivalent amount of inescapable foot shock 4 hr prior to the session of inescapable shock did not influence the occurrence of the second analgesic reaction. This indicates that the escapability of the foot shock 4 hr prior to inescapable shock, and not foot shock per se was the important factor in preventing the second analgesic reaction that occurs following 80 inescapable shocks.

EXPERIMENT 2

Jackson et al. (1979) demonstrated that a long-term analgesic reaction could be induced in rats 24 hr following exposure to inescapable tail shock provided that the subjects were reexposed to shock immediately prior to testing. In other words, inescapable shock sensitized some analgesia-producing system, so that a small amount of shock 24 hr later was sufficient to produce an analgesic response.

Results reported by Grau et al. (1981) and Maier et al. (1980) suggest that initial activation of opioid analgesia systems is necessary for this sensitization or long-term analgesic reaction to occur. Grau et al. found that 60–80 inescapable shocks were necessary to produce a reinstatable analgesic reaction 24 hr later. Fewer shocks produced short-term, but no long-term, reinstatable analgesia. As noted earlier, 60–80 inescapable shocks are also necessary to produce the later occurring opioid analgesic reaction observed immediately following the shock session. Maier et al. (1980) prevented the occurrence of the long-term analgesic reaction to inescapable shock by administering the opiate antagonist naltrexone prior to the session of shock. Such a manipulation also prevents the occurrence of opioid analgesia during a session of inescapable shock (Grau et al., 1981). Thus, treatments which block activation of the opioid analgesia system also prevent sensitization of that system.

Experiment 1 in the present study shows that prior shock–escape training prevents the occurrence of an analgesic response immediately following 80 inescapable shocks. Moye et al. (1981) demonstrated that escapable shock prior to inescapable shock also blocks the long-term analgesic reaction. Together, the present Experiment 1 and the results of Moye et al. (1981) suggest that prior escapable shock prevents activation
of opioid analgesia systems by subsequent inescapable shock. However, it is not known how prior escape training is having such an effect.

Maier et al. (1982) suggested that the learning that shock is uncontrollable might be an important factor in producing opioid analgesia. As mentioned earlier, prior escape training could interfere with such learning and thus prevent the release of endogenous opioids. On the other hand, escape training could have a more direct effect on the mechanisms producing opioid analgesia independent of interference with the learning of uncontrollability. It is possible that experience with escapable shock may activate a physiological process that is directly antagonistic to the activation of opioid analgesia systems. If escapable shock is having an effect by the activation of an antagonistic physiological process rather than interfering with the learning of uncontrollability during a subsequent session of inescapable shock, escape training might also be able to mitigate the effects of activation of opioid analgesia mechanisms produced by administration of an exogenous opiate such as morphine.

In order to address these possibilities, Experiment 2 examines the effect of prior shock–escape training on the long-term analgesic reaction produced by morphine. Grau et al. (1981) have previously demonstrated that a long-term analgesic reaction can be induced in rats by substituting a single injection of the opiate agonist morphine for a session of inescapable tail shock. In the Grau et al. (1981) study, one group of rats was injected with morphine (4 mg/kg, subcutaneous), while another group received only the saline vehicle. Twenty-four hours following the injection, half of the subjects received 5 brief foot shocks followed immediately by tail-flick analgesia testing. The other subjects were given the tail-flick tests with no prior shock. The results were that only animals which received morphine and the 5 brief shocks displayed an analgesic response. This suggests that morphine, like inescapable tail shock, may sensitize an opioid system responsible for producing an analgesic response upon later exposure to brief shock.

In the following experiment, different groups of rats are given escapable, inescapable, or no shock in shuttleboxes as in Experiment 1. Four hours later, the rats received a single injection of morphine in place of the session of inescapable tail shock. Twenty hours following the injection, all subjects received 5 brief foot shocks and were then immediately given 3 tail-flick analgesia tests.

If the effect of escape training is such that it interferes with learning that shock is uncontrollable during the subsequent session of inescapable shock, this treatment should have no effect on morphine-induced sensitization since here the opiate is administered exogenously. However, if the effect of escape training is more direct, such that it results in activation of some process antagonistic to opioid analgesic and/or sensitization processes, or alters some nonopioid mechanism critical in the
production of opioid sensitization, this treatment should prevent morphine-induced sensitization.

Method

Subjects. The subjects were 48 rats of the same sex, strain, age, and weight as in Experiment 1. Housing conditions and time of experimental sessions were also the same as in Experiment 1.

Apparatus. Escapable foot shock, yoked inescapable foot shock, or restraint was carried out in the same two-way shuttleboxes as described in Experiment 1. The brief, reinstating shocks administered immediately prior to tail-flick analgesia testing were also administered in the shuttleboxes. Analgesia testing employed the same tail-flick device as in Experiment 1.

Procedure. The subjects were randomly assigned to one of six groups (n = 8/group). Subjects in Groups EM and ES were given 48 escape/avoidance trials (24 FR-1 and 24 FR-2) in the shuttleboxes as in Experiment 1. Subjects in Groups YM and YS were each assigned a partner in Groups EM and ES, respectively. The YM and YS subjects received equal amounts of uncontrollable shock as their partners in Groups EM and ES. Subjects in Groups RS and RM were merely restrained in the shuttleboxes for periods of time equal to that of subjects in Groups EM and ES.

Four hours after the end of the shuttlebox session, subjects in Groups EM, YM, and RM were given a single subcutaneous (sc) injection of morphine sulfate (4 mg/kg) in normal saline. Subjects in Groups ES, YS, and RS received a single sc injection of an equivalent volume of saline alone. Subjects in all groups were tested 20 hr following the injection. The test procedure consisted of exposing the subjects to five 0.6-mA inescapable foot shocks of 5-sec duration in the shuttleboxes. The shocks were presented on a 60-sec variable time schedule (range 5–150 sec). Following the 5 shocks, each subject received three tail-flick test trials. On each trial, the experimenter (who was unaware of group membership) held the subject in his/her hand, and placed the subject’s tail in the grooved metal plate. A switch activated the lamp and started a timer. The light beam was focused on a spot about halfway between the base and tip of the tail. The heat was adjusted as in Experiment 1. After each test trial, the subject was returned to the shuttlebox for approximately 3 min.2

1 Groups given morphine followed 20 hr later by tail-flick testing without brief exposure to shock were not run in this experiment. Grau et al. (1981) clearly demonstrated that a long-term analgesic response to morphine was only observable if tail-flick testing was preceded by brief exposure to shock. Furthermore, the amount of shock given prior to tail-flick testing is not sufficient by itself to produce analgesia.

2 Groups ES and YS in this experiment were run several months following the testing of the other four groups at the suggestion of a reviewer.
Results and Discussion

The mean latencies to escape during the 48 shuttlebox escape trials were 8.8 and 9.1 sec for Groups EM and ES, respectively. These latencies did not differ reliably \([F(1, 14) < 1]\). The mean tail-flick latencies recorded following the 5 brief reinstating shocks are presented in Fig. 2. As can be seen, the subjects given a morphine injection preceded by no foot shock (Group RM) were much slower to tail-flick following reinstatement than subjects given only saline preceded by no foot shock (Group RS). This replicates the finding of Grau et al. (1981) that brief shock can elicit an analgesic reaction if preceded by a single injection of morphine. However, experience with escapable footshock 4 hr prior to the morphine injection prevented the analgesic response from occurring 20 hr later (Group EM). The analgesic response to morphine was not prevented by an equivalent amount of inescapable shock 4 hr prior to the injection (Group YM). This indicates that the escapability of the foot shock prior to the morphine injection was critical in preventing the analgesia normally observed following reinstatement. Additionally, it should be noted that neither the escapable or inescapable foot shock treatments were sufficient by themselves to produce an analgesic response 24 hr later following brief reexposure to shock. Groups given escapable (Group ES) or inescapable (Group YS) foot shock 4 hr prior to a saline injection produced tail-flick latencies no different than subjects given only restraint followed by saline (Group RS). It is not surprising that the shock session in the shuttlebox produced no long-term analgesia, as the shock intensity was lower than that usually required to produce reinstatable analgesic responses (0.6 rather than 1.0 mA).

![Fig. 2. Mean tail-flick latencies for subjects given escapable shock (EM and ES), yoked inescapable shock (YM and YS), or restraint (RM and RS) 4 hr prior to a single injection of morphine or saline. Twenty hours following the injection, all subjects were given 5 brief foot shocks immediately prior to tail-flick testing. The vertical lines indicate the standard errors of the means.](image-url)
Statistical analysis confirmed these impressions. Analysis of variance yielded a significant effect of Group membership \[F(5, 42) = 4.9\]. Subsequent Duncan's post hoc individual comparisons (\(\alpha = .05\)) indicated that Groups RM and YM did not differ from one another, but were reliably different from all other groups. Furthermore, Groups RS, YS, ES, and EM did not differ from one another. Thus, experience with escapable, but not inescapable shock 4 hr prior to a single morphine injection prevents the occurrence of an analgesic response 24 hr later after brief reexposure to shock.

**GENERAL DISCUSSION**

The present experiments examined the effects of prior experience with escapable shock on subsequent analgesic reactions produced by inescapable shock or morphine administration. In Experiment 1, it was demonstrated that experience with escapable foot shock 4 hr prior to a session of inescapable tail shock prevented the occurrence of the analgesic response normally observed following 80 shocks. Equivalent amounts of inescapable foot shock 4 hr earlier had no effect on the analgesic reaction following 80 shocks. Prior escapable or inescapable shock did not prevent the early analgesic reaction that occurs after relatively few (5 or 20) shocks. In fact, a significant analgesic reaction developed after fewer shocks for the groups given foot shock (escapable or inescapable) 4 hr before the session of inescapable shock. The group given inescapable foot shock 4 hr prior to the tail-shock session produced the longest latencies after 5 shocks. It is possible that the system responsible for the production of the early occurring analgesia was sensitized during the session of foot shock, and that inescapable foot shock had a stronger sensitizing effect than escapable foot shock.

In Experiment 2, escapable shock 4 hr prior to morphine administration prevented the long-term (20 hr) analgesic reaction observed following subsequent brief exposure to shock. Again, an equivalent amount of inescapable shock was ineffective in preventing the analgesic reaction. Thus in both experiments, the escapability of the foot shock prior to inescapable shock or morphine seemed to be the critical factor in preventing the development of the analgesic reactions.

It could be argued that the differences in tail-flick latency observed following 80 tail shocks in Experiment 1 do not reflect changes in pain reactivity, but are instead due to differences in rate of learning to escape from the noxious heat stimulus applied to the tail. A large number of experiments investigating the learned helplessness effect have clearly shown that experience with inescapable, but not escapable shock will interfere with the acquisition of subsequent instrumental escape/avoidance behavior (see Maier & Seligman, 1976). The tail-flick procedure certainly possesses an inherent instrumental component: An aversive stimulus is
applied to the tail and the subject responds to escape the stimulus. Thus it is possible that the group given prior inescapable foot shock produced long tail-flick latencies (as compared to subjects given prior escapable foot shock) following 80 tail shocks due to retarded learning of the contingency between the tail-flick response and removal of the noxious heat stimulus over the five analgesia testing trials. Alternatively, prior exposure to escapable shock might have facilitated such learning.

Although possible, an explanation based on differences in rate of learning to perform the tail-flick response seems unlikely to us for several reasons. First, the group given no foot shock prior to the tail-shock session also demonstrated tail-flick latencies significantly slower than subjects given prior escapable foot shock. Learned helplessness studies generally do not find differences between escapably shocked and nonshocked groups in rate of acquisition on instrumental escape/avoidance tasks. Second, studies employing multiple tail-flick trials in untreated control groups (e.g., Grau et al., 1981) generally find no decreases in latency to respond over many repeated trials, implying that learning may not be a significant factor in tail-flick latency. Of course, here latencies were long after 5 and 20 shocks, possibly facilitating learning. Finally, it is unlikely that a nonspecific positive transfer effect from foot shock to heat on the tail could be detected after only five test trials.

We have proposed elsewhere (see Grau et al., 1981; Maier et al., 1982) that the second analgesic reaction observed following 80 inescapable shocks is mediated in some fashion by endogenous opioid systems. Support for this assertion is found in experiments which have demonstrated that the analgesia that normally occurs following 80 inescapable shocks is reversed by the opiate antagonist naltrexone (Grau et al., 1981; Hyson et al., 1982) and that the analgesia produced by an extended period of inescapable shock is cross-tolerant with the opiate analgesic morphine (Drugan et al., 1981; Lewis, Sherman, & Liebeskind, 1981). Furthermore, we have suggested that the opioid analgesia produced by an extended period of shock is a consequence of the subject learning that the stressor is uncontrollable (Maier et al., 1982; Maier, Drugan, Grau, Hyson, MacLennan, Moye, Madden, & Barchas, in press). That is, during an extended session of inescapable shock, the subject learns that behavioral coping is ineffective, and this learning of uncontrollability in the stressful situation triggers the activation of an endogenous opioid analgesia system. In Experiment 1, the analgesia normally observed following a lengthy session of inescapable shock was prevented if the subjects had prior experience with escapable shock. These results suggest that learning that shock is controllable interferes with subjects later learning that inescapable shock is, in fact, uncontrollable. If subjects do not learn that the shock is uncontrollable, then the opioid analgesia system may not become activated in response to the shock.
The results of Experiment 2, however, suggest a more direct effect of prior escapable shock on the activation and/or sensitization of opioid analgesia systems, since the sensitization examined here was produced pharmacologically by morphine rather than inescapable shock. Recall that experience with escapable shock 4 hr prior to an injection of morphine prevented the occurrence of an analgesic response 20 hr later following brief exposure to shock. The escapable shock prevented the morphine from having its sensitizing effect on the analgesia produced by shock. This result suggests that escapable shock may prevent subsequent shock-induced or morphine-induced analgesia by directly interfering with the activation or sensitization of opiate analgesia systems. It has been suggested (see, for example, Margules, 1979) that organisms possess endogenous mechanisms that work antagonistically to the actions of opioid systems, operating in effect like endogenous naloxone. Perhaps such an opioid-antagonistic system is activated by experience with escapable shock, and opposes the later activation or sensitization of that system by inescapable shock or exogenously administered opiates.

The data of Experiment 2 also provide further evidence that the long-term analgesic reaction that occurs 24 hr following inescapable shock (Jackson et al., 1979; Maier et al., 1980) is produced through activation of an opioid analgesia system. Moye et al. (1981) demonstrated that experience with escapable shock prior to inescapable shock could prevent this long-term analgesic reaction. In Experiment 2 in the present study, the analgesic reaction that can be observed 24 hr following activation of opioid systems by morphine was similarly blocked by prior experience with escapable shock. Since the sensitization produced by either shock or morphine are both influenced in the same manner by the same treatment (prior escapable shock), common mechanisms in producing the shock- or morphine-induced long-term analgesia are likely to be involved.

Thus, experience with escapable shock prior to a session of inescapable shock or morphine administration can influence the nature of the analgesic responses produced by these two treatments. These results suggest that experiencing control over a stressor such as shock may trigger physiological reactions that oppose the activation of opioid analgesia systems.

REFERENCES


Margules, D. L. Beta-endorphin and endoloxone: Hormones of the autonomic nervous system for the conservation or expenditure of bodily resources and energy in anticipation of famine or feast. *Neuroscience and Biobehavioral Reviews*, 1979, 3, 155–162.


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