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The Opioid/Nonopioid Nature of Stress-Induced Analgesia and Learned Helplessness

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Exposure to a variety of stressors produces a subsequent analgesic reaction. This stress-induced analgesia (SIA) is sometimes opioid in nature (reversed by opiate antagonists and cross-tolerant with morphine) and sometimes nonopioid. Both 30 min of intermittent footshock and 60–80 five-sec tailshocks have been shown to produce opioid SIA, whereas 3 min of continuous footshock and 5–40 tailshocks produce nonopioid SIA. We report that both of the opioid SIA procedures produce a learned helplessness effect as assessed by shuttlebox escape acquisition and an analgesia that is reinstatable 24 hr. later. The nonopioid procedures produce neither a learned helplessness effect nor a reinstatable analgesia. It is argued that these data implicate the learning of uncontrollability in the activation of opioid systems.

There exist well-defined neural systems capable of blocking pain transmission. These systems are of interest because their operation depends, at least in part, on an endogenous opioid peptide(s) (see Basbaum & Fields, 1978, and Sherman & Liebeskind, 1980, for reviews). The existence of such systems has created considerable interest in the environmental events that might activate them. Hayes, Bennett, Newlon, and Mayer (1978) reported that brief footshock, intraperitoneal hypertonic saline injection, and centrifugal rotation all produced a marked analgesic reaction. Decreases in pain sensitivity/reactivity have subsequently been demonstrated following exposure to a variety of events (cold water swims, immobilization, food deprivation, 2-deoxyglucose injections, tailshock, etc.) using a large number of different pain measures (tail-flick to radiant heat, hot plate paw lick latencies, vocalization, flinch-jump test, etc.). This phenomenon has come to be called stress-induced analgesia (SIA) because all of the events that produce decreases in pain sensitivity/reactivity measures appear to be stressors. Reviews of this literature can be found in Amir, Brown, and Amit (1980), Bodnar, Kelly, Brutus, and Glusman (1980), Chance (1980), and Watkins and Mayer (1982).

The occurrence of naloxone-sensitive SIA, coupled with the finding that SIA covaries with increased opioid levels (Madden, Akil, Patrick, & Barchas, 1977), led to the notion that stress might release endogenous opioids, thereby activating midbrain inhibitory systems. Unfortunately, manipulations designed to assess the involvement of endogenous opioids in the production of SIA have had inconsistent effects. This state of affairs suggests that there are both opioid and nonopioid mechanisms of pain inhibition. A critical question then becomes the nature of the experiential events that selectively determine whether opioid or nonopioid mechanisms of pain inhibition are activated.

Lewis and his colleagues suggested that the temporal characteristics of stressful events may be one critical determinant. They found that a 20–30-min exposure to intermittent footshock (1 sec of shock every 5 sec) pro-

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duced an opioid form of analgesia; it was blocked by prior administration of naloxone and was cross-tolerant with morphine. In contrast, a 3-min exposure to continuous footshock resulted in a nonopioid form, because it was unaffected by naloxone and not cross-tolerant with morphine (Lewis, Cannon, & Liebeskind, 1980; Lewis, Sherman, & Liebeskind, 1981). Thus, the same stressor—footshock—delivered with different temporal parameters can selectively determine opioid or nonopioid mediation of SIA.

Grau, Hyson, Maier, Madden, and Barchas (1981) and Hyson, Ashcraft, Drugan, Grau, and Maier (1982) found that the number of inescapable shocks is a critical feature in activating opioid SIA. Naltrexone, an opiate antagonist, did not diminish the analgesic response measured after 5 or 20 inescapable tailshocks (5-sec shocks occurring on the average of one every min). However, naltrexone completely blocked the analgesia observed after 60 or 80 shocks of exactly the same type. Moreover, exposure to the 80 tailshocks sensitized the organism such that exposure to a small amount of footshock 24 hr. later in a different apparatus reinstated the analgesic reaction (Jackson, Maier, & Coon, 1979). This long-term reinstated SIA was also completely blocked by opiate antagonists (Maier et al., 1980) and was cross-tolerant with morphine (Drugan, Grau, Maier, Madden, & Barchas, 1981). This reinstated SIA was only observed following the initial shock conditions that activated the opioid form of SIA (60 or 80, but not 20 or 40 tailshocks).

However, simple exposure to a large number of shocks is not sufficient to produce opioid SIA. Instead, it is important that the shocks be inescapable and unavoidable. Maier, Drugan, and Grau (1982) gave rats identical amounts and distributions of escapable or inescapable tailshocks. The groups differed only in availability of an instrumental response to terminate the shocks. Both types of shock produced an immediate short-term SIA, but the analgesia following inescapable shock was more sensitive to naltrexone. Moreover, the long-term reinstated analgesia only occurred following inescapable shock; here, escapable shock was without effect (Jackson et al., 1979). This set of data led Maier and his colleagues to conclude that the organism's learning that it had no control over shock might be a critical factor in activating opiate systems. That is, what the organism learns about the stressor, rather than the simple physical features of the stressor, might be crucial.

The apparent importance of the controllability of the stressor in the production of SIA suggests a relationship between SIA and another behavioral phenomenon in which controllability is important, namely, learned helplessness. Exposure to inescapable shock interferes with subsequent learning to escape from shock in a different situation, whereas experience with equal amounts of escapable shock does not have this effect. This is called the *learned helplessness effect* (Overmier & Seligman, 1967), and according to the learned-helplessness hypothesis (cf. Maier & Seligman, 1976), learning that shock cannot be controlled activates the processes leading to this effect.

If learning that shock is inescapable or uncontrollable is an important factor in activating opioid processes, it would be expected that a large number of shocks are required. Learning that shock is not escapable is a complex form of learning and ought to take many trials. Consistent with this argument, the learned-helplessness effect requires experience with a large number of shocks (Anisman, Remington, & Sklar, 1979). The notion that the learning of inescapability or uncontrollability might be a critical factor in activating opioid SIA might also be relevant to the Lewis et al. (1980) and Lewis, Sherman, and Liebeskind (1981) findings. A 3-min. exposure to shock, which Lewis, Cannon, and Liebeskind (1980) found to produce nonopioid SIA, might be insufficient to allow the organism to learn that the shock cannot be controlled. In contrast, their 20–30 min. exposure condition might be enough to allow such learning to occur.

The argument is *not* that SIA produces the shuttlebox escape learning deficit. Indeed, we know that this is not the case (MacLennan et al., in press; Mah, Suissa, & Anisman, 1980). The argument is only that the same factor(s) that activate the processes that produce escape interference might also activate processes leading to opioid SIA.

This argument is testable in a variety of ways. Perhaps the most obvious implications of the above reasoning is that both the Lewis et al. (1980) 20–30-min. intermittent-footshock procedure and the Grau et al. (1981) 60–80 tailshock procedure should produce the standard behavioral learned helplessness effect. Neither the 3-min. continuous-shock nor 20–40 tailshocks should produce such an effect. In addition, the 3-min. continuous- and the 30-min. intermittent-footshock procedures ought to produce other differences similar to those that appear after 20 and 60–80 tailshocks. For example, 60 and 80 tailshocks lead to an analgesia that can be readily reinstated 24 hr. later by brief stress, whereas 20 shocks do not lead to a reinstatable analgesia (Grau et al., 1981). Similarly, the 30-min. intermittent-footshock SIA ought to be reinstatable, whereas the 3-min. continuous-footshock SIA should not be reinstatable 24 hr. later. The purpose of the present experiments was to test these predictions.

Experiment 1

The above discussion suggests that procedures that produce opioid SIA might also produce a learned helplessness effect on the standard test tasks used in such experiments. In contrast, procedures that produce nonopioid analgesia might not lead to such an outcome. In Experiment 1, we compared the ability of the two shock procedures used by Lewis et al. (1980) to produce a learned helplessness effect. We employed the same apparatus used by Lewis and his colleagues to produce SIA and the apparatus used by Maier and his colleagues to assess learned helplessness. The test for learned helplessness consisted of 5 shuttlebox escape trials that required the subject to cross once to terminate shock, followed by 25 shuttlebox trials that required two crossings (FR-2). This is a standard test for learned helplessness (see Maier, Albin, & Testa, 1973, for a rationale). Inescapably shocked subjects typically respond rapidly on the single-crossing shuttlebox trials, but fail to learn the FR-2 escape. Thus, one group received the Lewis et al. 3-min. continuous procedure, another received the 20-min. intermittent procedure, and a third group was merely placed in the apparatus. As in the typical learned helplessness experiment, the subjects' escape behavior was assessed 24 hr. later. A final two groups duplicated the usual learned helplessness groups so that the magnitude of any effect found could be determined.

Method

Subjects. The subjects were 40 male albino rats obtained from the Holtzman suppliers in Madison, Wisconsin. The rats were 85–95 days of age at the start of the experiment. They were maintained on a 12-hr. light/12-hr. dark cycle, and food and water were continuously available. Experimentation occurred during the light phase of the cycle.

Apparatus. Footshocks were administered through the grid floor of a 23 × 23 × 20 cm Plexiglas chamber. The inescapable footshock was scrambled 2.5-mA 60-Hz sine waves. This is the apparatus used by Lewis et al. (1980).

Inescapable tailshocks or restraint occurred in Plexiglas restraining tubes that were 23.4 cm long and 7.0 cm in diameter. Each rat's tail extended from the rear of the tube and was taped to a Plexiglas rod. Unscrambled shocks were delivered through electrodes attached to the rat's tail and augmented with electrode paste. Shock intensity was 1.0 mA. This is the apparatus used by Maier and his colleagues in learned helplessness experiments.

Escape training was carried out in four two-way shuttleboxes that measured 34.5 × 20.5 × 19.5 cm. The boxes were divided into two compartments of equal size by a metal sheet that spanned the width of the box from floor to ceiling. An archway 5.5 cm high and 5.5 cm wide was cut from the center of the metal sheet. Thus, the rats could cross from one side of the shuttlebox to the other only by passing through this archway. Scrambled shocks were delivered to the grid floor by shockers modeled after the Grason–Stadler Model 700. Shock intensity was .6 mA.

Procedure. The 40 subjects were randomly divided into five groups. The first two groups received treatment identical to that used by Lewis et al. (1980). One group of rats (3-C) was given 3 min of continuous footshock using the shock parameters described above. The second group (20-I) received 20 min of intermittent footshock on a 1-sec on, 5-sec off schedule. A third group (AC) served as an apparatus control group. These subjects were merely placed in the shock apparatus without being shocked. Half of the subjects were confined for 3 min and half for 20 min. The final two groups duplicated groups used in learned helplessness experiments. One group (80-T) received 80 five-sec 1.0-mA shocks delivered to the tail on a variable interval 60-sec schedule. The final (RC) group served as a restrained control group. They were merely restrained in the shocking tubes for a period of time equal to that taken by the 80-T procedure.

All subjects were given shuttlebox escape/avoidance training 24 hr. later. Shuttlebox trials were presented on a variable-time 60-sec schedule. At the beginning of a trial, a 1000-Hz tone was sounded that raised the background noise level from approximately 70 to 75 dB (re

20 $\mu N/m^2$). If a response did not occur within 5 sec, a .6-mA shock was applied to the grid floor, and the tone and shock terminated whenever a response occurred. The trial terminated automatically if no response had occurred within 35 sec of the onset of the tone, and a 35-sec latency was recorded. During the first five trials, shock could be escaped from or avoided if the animal simply ran from one side of the shuttlebox to the other (FR-1). During the next 25 trials, shock could be escaped from or avoided if the animal crossed the shuttlebox twice (FR-2), that is, the rats were required to cross from one side of the box to the other and then return.

A rejection criterion of $p < .05$ was used in all tests of statistical significance.

Results and Discussion

The results presented in Figure 1 show the mean shuttlebox response latency from tone onset for each of the five groups in blocks of five trials. The first point represents the five FR-1 trials and indicates somewhat longer escape latencies for the groups given 80 tailshocks and 20 min. of intermittent footshock than for any of the other groups. The two control groups and the group given 3 min. of continuous shock did not appear to differ. These conclusions are confirmed by an analysis of variance (ANOVA) that yields a reliable groups effect, $F(4, 35) = 3.62$.

Figure 1 also shows the results of the FR-2 trials, the test on which the learned helplessness effect is normally observed. As expected, the groups given 80 tailshocks and 20-min intermittent footshocks performed poorly. Recall that a 35-sec latency was recorded if the subject failed to escape by the time the trial terminated. Thus, the fact that the mean latencies for these two groups were approximately 30 sec indicates that most of the animals in these two groups failed to escape at all on most of the trials. In contrast, the performance of the group given 3 min of continuous footshock was indistinguishable from that of the nonshocked control groups. A repeated measures ANOVA revealed reliable effects of groups, $F(4, 35) = 10.85$, trial blocks, $F(4, 140) = 6.49$, and the interaction of groups and trial blocks, $F(16, 140) = 3.13$. Post hoc Newman-Keuls tests indicated that the 20-min intermittent footshock and the 80-tailshock groups differed reliably from each of the other groups but did not differ from each other. The 3-min continuous footshock and the two control groups did not differ reliably from each other.

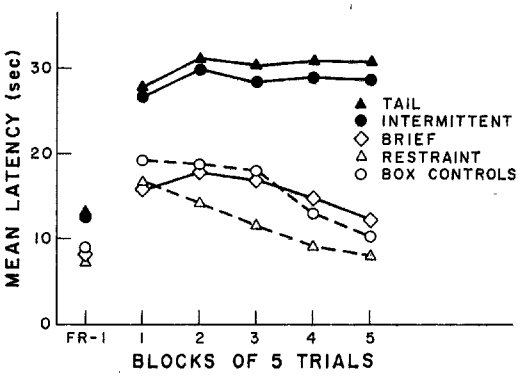

Figure 1. Mean shuttlebox response latency for groups given 80 tailshocks (tail), 20 min. of intermittent footshock (intermittent), 3 min. of continuous footshock (brief), restraint (restraint), or confinement (box controls).

Thus, the data clearly indicate that the Lewis et al. (1980) procedure, which produces opioid SIA, also produces a robust learned helplessness effect 24 hr. later. Moreover, the learned helplessness effect that emerged was as large as that produced by the procedure typically used to study it. Thus, both opioid-mediated SIA procedures also produce learned helplessness. Importantly, the Lewis et al. (1980) procedure that produces nonopioid SIA had no detectable effect on shuttlebox performance. Thus, the results of Experiment 1 are consistent with the hypothesis that there is a close relationship between opioid SIA and learned helplessness.

Experiment 2

The previous experiment assumed that the 20-min. intermittent shock procedure used would produce an opioid SIA and that the 3-min. continuous footshock condition would produce nonopioid SIA. That is, we assumed that the usual Lewis et al. (1980) results would have occurred. However, the experiment was conducted in a different laboratory with a different strain of rats housed under somewhat different conditions. Moreover, the Lewis et al. experiments were conducted during the dark phase of the rat's light/dark cycle, whereas the present experiment occurred during the light phase. This is not a trivial consideration, because a number of opioid effects are known to be sensitive to this variable (Frederickson, 1978). Thus, it is not certain that the SIA measured after the 20-min.

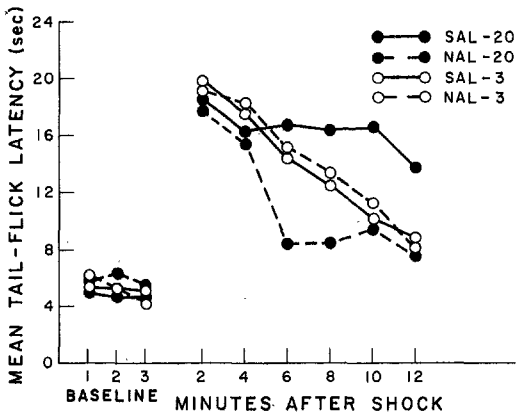

Figure 2. Mean tail-flick latencies for groups given either naltrexone (nal) or saline (sal) 20 min. before 20-min. intermittent (20) or 3-min. continuous (3) footshock.

procedure used here would have been blocked by opiate antagonists and that the SIA measured after the 3-min. procedure would not have been so blocked.

Experiment 2 thus examined the effects of an opiate antagonist on the SIA following the two Lewis et al. (1980) procedures as conducted in this laboratory in the preceding experiment. Also of interest were the particular opiate antagonist and dose used. Lewis et al. found that doses of naloxone ranging from .1 to 10 mg/kg blocked their opioid SIA, whereas Grau et al. and Hyson et al. used naltrexone in doses ranging from 1.75 to 28.0 mg/kg. Doses from 7.0 to 28.0 mg/kg of naltrexone were effective in blocking the opioid SIA. It is thus unknown whether the same antagonist at a similar dose would be effective with the two opioid procedures used by Lewis et al. (1980) and Grau et al. (1981). Such an outcome should occur if the two procedures are affecting the same processes in the same way. Thus, in this case, the drug and dose known to be effective in eliminating the 80 tailshock-induced opioid SIA were tested for their effects on the SIA produced by the two Lewis et al. procedures.

Method

Subjects. The subjects were 36 rats of the same sex, age, and strain as in the previous experiment. Housing and maintenance conditions were also unchanged.

Apparatus. Footshock was administered in the same apparatus described previously. SIA was assessed with a tail-flick apparatus. The tail-flick test device consisted of a metal box 43.0 cm long × 17.7 cm wide × 8.0 cm high that supported an aluminum plate 7.4 cm long × 3.0 cm wide. A shallow groove was cut in this plate, and each rat's tail was placed in this slot. The rat was restrained in a tube. A General Electric 150-W projector spotlight was mounted above the plate that held the rat's tail. A condenser lens was located between the tail and the light source and focused the light. A 3–5-mm deflection of the tail activated a photocell and automatically terminated the trial.

Procedure. The rats were divided into four groups. Two groups of 10 rats each received the 20-min intermittent-footshock procedure previously described, whereas two groups of 8 subjects each received the 3-min continuous-shock procedure. One of each of these groups received a 7 mg/kg subcutaneous injection of naltrexone 20 min before the shock treatment, whereas the other two groups received an equivalent volume injection of saline. Three baseline tail-flick tests were given immediately before the shock session with an approximate 2-min interval between tests. Further tail-flick tests were conducted 2, 4, 6, 8, 10, and 12 min following the shock session. The rats were restrained in holding tubes during tail-flick testing. Tail-flick trials were automatically terminated if a response did not occur within 20 sec.

Results and Discussion

The mean tail-flick latencies for each group on each test are shown in Figure 2. Both the 3-min continuous- and the 20-min intermittent-footshock procedures produced a large initial analgesic reaction, with almost all subjects going to the 20-sec cutoff. However, the analgesic response dissipated much more rapidly following the 3-min continuous-shock treatment. The subjects in the 20-min condition that had received saline were still markedly analgesic 12 min after the shock session, whereas the subjects in the 3-min shock condition displayed tail-flick latencies only 3–4 sec above baseline. Naltrexone appeared to have no effect on the responding of the subjects that had received 3 min of continuous footshock. In contrast, naltrexone exerted a powerful effect on the tail-flick responding of the subjects that were given the 20-min intermittent-footshock treatment. In this case, naltrexone greatly reduced the SIA effect. It should be noted that this effect of naltrexone did not appear until 6 min after the end of the shock session. Naltrexone had no effect on the latencies measured at the 2- and 4-min tests.

These conclusions were confirmed by a repeated measures ANOVA. It yielded reliable

effects for the following: naltrexone, $F(1, 32) = 6.61$, the Naltrexone × Shock Condition interaction, $F(1, 32) = 7.44$, time of testing, $F(5, 160) = 22.06$, the Naltrexone × Time of Testing interaction, $F(5, 160) = 2.30$, and the three-way Time of Testing × Naltrexone × Shock Condition interaction, $F(5, 160) = 4.22$. Post hoc Newman-Keuls tests indicated that the group given saline and the 20-min. intermittent-shock treatment differed reliably from all of the other groups and that both the saline and naltrexone 3-min. continuous-shock groups differed from the naltrexone 20-min. continuous-shock group but did not differ from each other.

Experiment 2 thus confirmed that under the conditions used in the present studies, the Lewis et al. (1980) 20-min. intermittent-footshock condition produces SIA sensitive to opiate antagonists, whereas the 3-min. continuous-condition produced an SIA not sensitive to opiate antagonists. This result was obtained in a different laboratory using a strain of rats, housing conditions, test apparatus and procedures, opiate antagonist, and dose different from those used by Lewis et al. (1980). Thus, Lewis et al.'s result appears to have considerable generality. In addition, these results demonstrate that the procedures used in the preceding experiments induced opioid and nonopioid SIA as intended.

The present results also highlight a number of features of the SIA produced by these procedures. Even though the initial analgesic reaction resulting from both procedures was maximal, dissipation of analgesia was much more rapid following the 3-min. continuous-shock condition. Even though 20 min. of intermittent footshock produces a longer lasting SIA, naltrexone makes this treatment more sensitive to the radiant heat than the less-effective 3-min. continuous-shock treatment. This strengthens the conclusion that the two procedures induce SIAs that depend on different processes. Naltrexone reduced the tail-flick latencies produced by the 20-min. intermittent shock to a level below that induced by the 3-min. treatment, which suggests that the 20-min. treatment does not involve a significant nonopiate component.

Experiment 3

The argument that we have made requires that the Grau et al. (1981) opioid SIA procedure (60 and 80 tailshocks) produces a learned helplessness effect and that the Grau et al. nonopioid procedure (20 and 40 tailshocks) does not. This parametric information is not known. Although we know that the number of inescapable shocks is an important determinant of learned helplessness effects (Anisman et al., 1979), existing studies used a different species, shock intensity, and shock duration.

The purpose of this experiment was to assess whether the Grau et al. shock procedures that produce opioid SIA also produce a learned helplessness effect and whether the procedures that produce nonopioid SIA do not. Rats were restrained in the tubes used by Grau et al. and given either 20, 40, 60, or 80 tailshocks with parameters identical to those used by Grau et al. Shuttlebox testing occurred 24 hr. later.

Method

Subjects. The subjects were 40 rats of the same age, sex, and strain as in Experiment 1. Housing conditions were also the same.

Apparatus. The same apparatus as in Experiment 1 was used.

Procedure. The subjects were randomly assigned to one of five groups. Four groups received either 20, 40, 60, or 80 inescapable tailshocks with the same parameters used in Experiment 1. The fifth group was merely restrained in the shocking tubes for a time equal to the 80-shock condition (87 min.). All subjects received escape/avoidance training in the shuttlebox 24 hr. later. The procedure was the same as in Experiment 1.

Results and Discussion

The results are shown in Figure 3, which plots the mean latency to respond for each group across blocks of five trials. As expected, the groups do not appear to differ on the FR-1 trials. This is supported by an unreliable groups effect ($F < 1.0$). In contrast, the FR-2 trials revealed large group differences. The subjects given 60 and 80 inescapable shocks escaped poorly, whereas the groups given 20 and 40 inescapable shocks did not differ from the restrained control group. It might be noted that restraint does not affect shuttlebox escape 24 hr. later using the present task

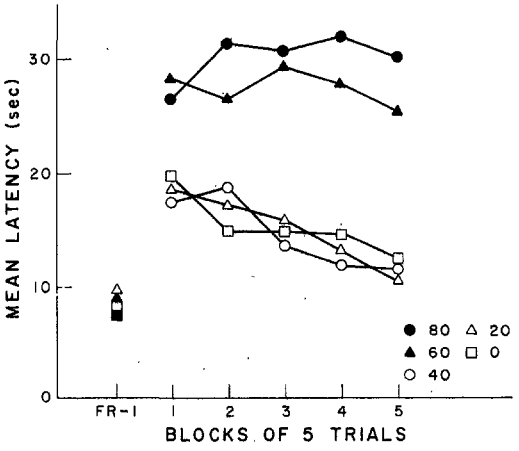

Figure 3. Mean shuttlebox response latencies for groups given 0, 20, 40, 60, or 80 inescapable tailshocks.

(Maier et al., 1973). In addition, the group given 80 shocks performed more poorly than the group given 60 shocks. This difference is not attributable to each subject in the 80-shock group performing slightly more poorly than those in the 60-shock group. Instead, more subjects failed to learn in the 80-shock group. Six of the eight subjects in the 80-shock group failed to escape on most of their FR-2 trials, whereas only four of the eight subjects in the 60-shock group failed to escape. These impressions were confirmed by a repeated measures ANOVA that yielded reliable effects for groups, $F(4, 35) = 9.26$, trials, $F(4, 140) = 4.03$, and the interaction of groups and trials, $F(16, 140) = 3.98$. Post hoc Newman-Keuls comparisons revealed that the 60- and 80-shock groups differed from the other three groups but did not differ from each other.

Thus, Experiment 3 indicates that the inescapable-shock conditions that produced opioid SIA in Grau et al. (1981) and Hyson et al. (in press) also produce a learned helplessness effect. In contrast, the conditions that produced either no analgesia or nonopioid SIA did not produce a learned helplessness effect. Thus, both the footshock and tailshock procedures that produce opioid SIA produce learned helplessness.

The notion that the Grau et al. (1981) and the Lewis et al. (1980) procedures activate the same processes requires that the two sets of procedures produce other similar outcomes. A finding of special interest for SIA concerns reactivation of the analgesic response. SIA experiments typically measure pain sensitivity/reactivity for some relatively short period following the stress exposure, normally 1 hr or less. The usual finding is that the analgesic response dissipates rapidly, returning to baseline in 15–30 min. Jackson et al. (1979) reported the novel finding that analgesia on both hot plate and tail-flick tests could be produced 24 hr. after exposure to inescapable tailshocks if the subjects were given a small amount of footshock, an amount insufficient to induce an analgesic response. The inescapable-shock conditions used by Jackson et al. were the same as those Grau et al. (1981) and Hyson et al. (1982) found produced opioid SIA. This led Grau et al. to compare the reinstatability of opioid and nonopioid SIA. Subjects were given either 0, 20, 40, 60, or 80 inescapable tailshocks. They were given a small amount of footshock 24 hr. later and pain sensitivity was assessed. Only the groups given 60 and 80 shocks became analgesic.

Experiment 4

The purpose of this experiment was to determine whether Lewis et al.'s (1980) opioid and nonopioid analgesia-inducing procedures would prove differentially reinstatable 24 hr. later. Thus, rats were exposed to either 3 min. of continuous or 20 min. of intermittent footshock. They were exposed to a small amount of footshock 24 hr. later, and tail-flick responding was assessed using the testing procedure and apparatus used by Lewis and his colleagues. This experiment thus tested the generality of the unique reinstatement finding and explored another possible point of similarity between the differing opioid/nonopioid procedures.

Method

Subjects. The subjects were 24 male Sprague-Dawley rats, weighing 400–450 gm at the start of the experiment. They were maintained on a 12-hr. light / 12-hr. dark cycle and were tested during the dark phase of the cycle. Food and water were continuously available.

Apparatus. Shocks were delivered in the grid boxes previously described. Tail-flick testing utilized a different apparatus. It consisted of a 5 × 8 × 13 cm aluminum box containing a projector bulb (Sylvania, 500 W, 120

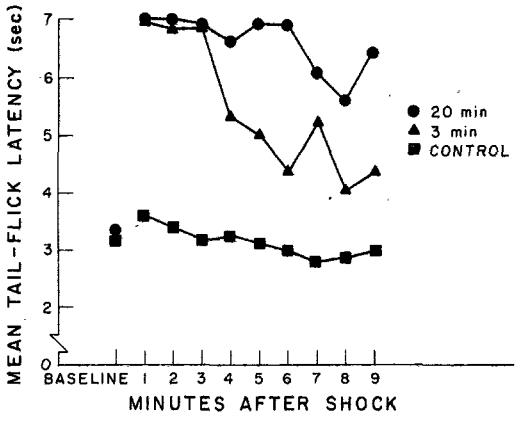

Figure 4. Mean tail-flick latencies following 20 min. of intermittent footschock (20 min), 3 min. of continuous footschock (3 min), or confinement to the apparatus (control).

V) mounted beneath a 6-mm diameter circular opening in the top surface. The bulb served as a source of radiant heat, and the temperature was adjustable as a function of the input voltage.

Procedure. The subjects were randomly assigned to three groups. All subjects were first tested for baseline pain responsiveness with five tail-flick tests each separated by 1-min intervals. The rats were loosely restrained in Plexiglas tubes with their tails extending from the rear. The caudal portion of the tail was placed over the aperture in the testing box and the radiant heat stimulus was applied. A trial was automatically terminated after 7 sec if the subject had not removed its tail. Following baseline testing, one group received 20 min of intermittent footshock using the procedure already described. A second group was placed in the shockbox for 17 min without shock, followed by 3 min of continuous footshock as previously described. Animals in the third group were placed in the test chamber for 20 min without shock. Nine tail-flick tests, at 1-min intervals, immediately followed the 20 min spent in the chamber.

All subjects were again given baseline testing 24 hr. later. They then received 30 sec of intermittent footshock using the same parameters described above. That is, shock was 2.5 mA in intensity and was presented on a 1-sec on 5-sec off schedule. The shock reexposure was followed by nine tail-flick trials at 1-min intervals. A maximum of 7 sec was allowed on all tail-flick tests.

Results and Discussion

Figure 4 shows the mean tail-flick latencies for the baseline period and for the measurements taken immediately after the shock session on Day 1. As can be seen, the groups did not differ during the baseline period. Both the 3-min. continuous-footshock and 20-min. intermittent-footshock procedures produced a pronounced analgesic reaction. This reaction was of similar magnitude in the two groups but dissipated more rapidly in the group that had received the 3-min. shock procedure.

The critical results are those from Day 2. Figure 5 shows the mean Day 2 baseline scores and those obtained following the shock reexposure procedure. The groups did not differ in baseline pain responsiveness. Thus, the subjects were not analgesic when tested 24 hr. after their shock experience. The important result was that the brief Day 2 shock exposure aroused an analgesic reaction in those subjects that had received 20 min. of intermittent footshock 24 hr. earlier, but the shock exposure had no impact on those subjects that had previously received 3 min. of continuous footshock. In addition, a comparison of Figures 4 and 5 indicates that the reinstated analgesia was smaller in magnitude than the original reaction was.

Because the Day 1 and Day 2 testing procedures were identical, these data were subjected to a single overall ANOVA with groups, days, and tests as factors. Groups, $F(2, 21) = 72.80$, days, $F(1, 168) = 200.7$, tests, $F(8, 168) = 12.88$, the Groups × Days interaction, $F(2, 168) = 43.92$, and the Groups × Days × Trials interaction, $F(16, 168) = 3.06$, were all statistically significant. Thus, as with the Grau et al. (1981) procedures, the Lewis et al. (1980) condition that yields opioid SIA is subject to reinstatement 24 hr. later, whereas the condition that results in nonopioid SIA

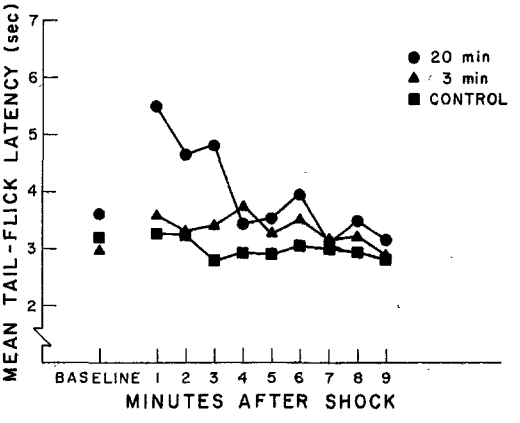

Figure 5. Mean tail-flick latencies following 30 sec of footshock 24 hr. after 20-min intermittent (20 min), 3-min continuous (3 min), or no shock (control).

is not. The present results also provide the new observation that the reinstated reaction is smaller than that which follows the original shocks. Grau et al. (1981) could not have observed such an outcome, because they only measured pain responsiveness after the reinstatement procedure.

General Discussion

The results of this series of experiments are clear. Both the 60–80 inescapable-tailshock procedure and the 20-min. intermittent-footshock procedure, which are known to produce opioid SIA, also produced a learned helplessness effect as assessed by the shuttlebox FR-2 escape acquisition. In contrast, both the 20–40 inescapable-tailshock and the 3-min. continuous-footshock procedures, which produce nonopioid SIA, have no effect on shuttlebox performance. As with the 60–80 tailshock procedure, 20 min. of intermittent footshock produced an analgesia reaction that was readily reinstated 24 hr. later. Similar to 20–40 inescapable tailshocks, 3 min. of continuous footshock did not lead to an analgesia that was reinstated by the shock conditions used.

The similarity in outcome of these procedures encourages the argument that they have their impact for the same reasons. Maier and his colleagues (Maier, Drugan, & Grau, 1982) provided evidence that the uncontrollability of shock is an important determinant of the SIA that follows their behavioral treatments. They argued that it is the organism's learning that it cannot control the stressor that might be the critical mediator. This suggests that the 3 min. of continuous shock is insufficient to lead to such learning. The absence of a learned helplessness effect here supports this argument.

It is not clear whether the learning-of-uncontrollability notion can account for all instances of opioid SIA. At least three procedures other than those used by Lewis et al. (1980) and Grau et al. (1981) have been shown to produce SIA strongly affected by opiate antagonists. Chesher and Chan (1977) reported that 10 min of footshock on a 10-sec on, 10-sec off schedule in mice produced an opioid SIA. Whether this condition would produce a learned helplessness effect in mice is unknown. However, exposure to as few as 30 shocks of 6-sec duration can produce a learned helplessness effect in mice (Anisman et al., 1979). Amir and Amit (1978) showed that a 30-min immobilization of rats can produce SIA reversed by naloxone. It might be noted that our restraint procedure produces neither SIA nor a learned helplessness effect. However, our restraining tubes fit over the rats loosely and do not restrict movement. In fact, the restrained control rats rarely struggle within the tubes or attempt to escape. Amir and Amit describe their restraining tubes as fitting snugly, thus restricting movement. The rats might well find this aversive and attempt to escape, thereby leading to the learning of uncontrollability. Whether immobilization more severe than that typically used in the Maier laboratory would produce a learned helplessness effect is unknown.

Although explanations of the above two findings with a learning-of-uncontrollability hypothesis is plausible, this sort of argument cannot reasonably be applied to a series of studies reported by Watkins, Cobelli, Farris, Aceto, and Meyer (in press). These investigators found that 90 sec of gridshock applied only to the forepaws of rats produced SIA that was reversed by naloxone and cross-tolerant with morphine. This same shock delivered only to the rear paws or to all four paws produced SIA unaffected by naloxone and not cross-tolerant with morphine. There is no obvious reason why this limited amount of forepaw shock should lead to the learning of uncontrollability, whereas the same amount of rear-paw or all-paw shock should not. However, it can be noted that the opioid SIA found by Watkins et al. in these studies is of a different type than that isolated by Grau et al. (1981) and Lewis et al. (1980). The opioid SIA that follows 80 inescapable tailshocks and 20 min of intermittent footshock is dependent on the integrity of the pituitary-adrenal system. Surgical removal of the pituitary or suppression of pituitary activity with dexamethasone completely blocks the SIA following 80 inescaple tailshocks (MacLennan et al., in press). Removal of the adrenal gland has the same effect (MacLennan et al., in press). Similarly, dexamethasone (Lewis et al., 1980), removal of the

pituitary (Lewis, Chudler, Cannon, & Liebeskind, 1981), and demedullation of the adrenals (Lewis, Tordoff, Sherman, & Liebeskind, 1982) all block the analgesia seen after 20 min of intermittent footshock. Removal of the pituitary also blocks the immobilization-induced SIA (Amir & Amit, 1979). In contrast, hypophysectomy has no effect on the SIA induced by the 90 sec of shock to the forepaws, and adrenalectomy actually potentiates the SIA that results (Watkins & Mayer, 1982). These results have led Watkins and Mayer (1982) to distinguish between neurally and hormonally mediated opiate SIA as different phenomena. The phenomenon that we have been addressing is clearly of the hormonal type, whereas that isolated by Watkins et al. is of the other type.

As already noted, we are not arguing that the analgesia that is produced by inescapable shock or the learning of uncontrollability is responsible for producing the learned helplessness effect. We are only suggesting that the same environmental or experiential factor(s) that is (are) responsible for activating one might also be important for the other. Learning that an aversive outcome cannot be controlled undoubtedly has many consequences and activates many different internal processes. Some of these internal processes could be responsible for the analgesia, whereas others might cause the shuttlebox escape acquisition deficit. At this time it is not possible to specify the reason why the learning of uncontrollability might activate opioid processes. Whether the cognition of no control does so directly, does so because it produces a large amount of "stress" (e.g., Weiss, 1968) or depletes or otherwise alters a particular transmitter system, and so forth, cannot be stated. It is also possible that the critical factor in the controllability/uncontrollability difference is not with regard to what the subject has learned about controllability in any direct way (Weiss, 1971). However, it can be noted that extremely "stressful" procedures, such as a 3.5-min. immersion in freezing water, which depletes transmitter substances such as norepinephrine (Stone, 1970), do not produce opioid SIA (Bodnar, Kelly, Spiaggia, Pavlides, & Glusman, 1978). As shown here, opioid SIA tends to be relatively long-lasting and is easily rearoused, and this might be particularly adaptive in uncontrollable aversive situations that have persisted long enough for the organism to have learned about its inability to exert control.

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