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Cross Tolerance Between Morphine and the Long-Term Analgesic Reaction to Inescapable Shock[1]

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DRUGAN, R. C., J. W. GRAU, S. F. MAIER, J. MADDEN, IV AND J. D. BARCHAS. *Cross tolerance between morphine and the long-term analgesic reaction to inescapable shock*. PHARMAC. BIOCHEM. BEHAV. **14**(5) 677–682, 1981.—Animals exposed to a variety of stressors display a temporary analgesic reaction. This short-term analgesia has been shown to be reversible by opiate antagonists and cross-tolerant with morphine following some stress conditions, but not following others. It has recently been shown that inescapable shock parameters which produce behavioral "learned helplessness" effects also produce a short-term analgesic reaction, and that this reaction can be re-aroused by a brief exposure to shock 24 hours later. Further, both the immediate and long-term antinociceptive reaction which follow shocks of this type have been shown to be reversible by opiate antagonists. Here it is shown that the long-term analgesic reaction is completely cross tolerant with morphine. Implications of these results for opioid mediation of learned helplessness and opioid versus nonopioid mediation of stress-induced analgesia are discussed.

Learned helplessness Morphine cross tolerance Stress-induced analgesia Endogenous opiates Inescapable shock

CONSIDERABLE recent attention has focused on physiological mechanisms which regulate pain. A variety of evidence [15, 20, 29] has led to the general view that the brain contains a midbrain system which descends to the spinal cord and inhibits ascending pain transmission. Further, this system seems to involve an endorphin or enkephalin-mediated process somewhere in the system, with release of an opioid substance being a critical step in the inhibition of pain by this system [29].

Although there is a large and growing body of literature concerning the anatomy, neurochemistry, and physiology of this pain modulation system, little effort has been directed at understanding the environmental or experiential factors which activate and control it. Correspondingly, little is known concerning the role which the system plays in behavior (for exceptions see [3, 7, 20, 26, 28].

A phenomenon which has come to be called "stress-induced analgesia" is one of the few which have been extensively studied in this regard. The term stress-induced analgesia refers to the fact that exposure to a variety of noxious stimuli produces an analgesic reaction which persists for 1–2 hours, as evidenced by a decrease in reactivity on a wide range of analgesimetric measures such as Formalin-induced writhing, hot plate, jump-flinch to shock, paw pressure analgesiometer, tail-flick to radiant heat, vocalization, etc. [1, 2, 4, 5, 16, 22]. Further, exposure to a previously neutral stimulus which has been associated with a painful stimulus can induce an analgesic reaction as well [10, 14, 21].

Nonopiate as well as opiate mechanisms are involved in the regulation of pain [18], and the system described above is not the only participant in pain regulation. Thus the fact that stressful events produce pain inhibition does not necessarily imply that they activate an opiate system. In fact, evidence on this issue is inconclusive. Exposure to shock has been shown to result in elevated central opioid levels as measured by radio-receptor binding assay [22]. Similarly, the antinociception induced by stimuli previously paired with shock is associated with decreased binding of (^{3}H) N-

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leu-enkephalin in brain [11], suggesting increased receptor occupancy by endogenous opiates. However, the influence of opiate antagonists has been inconsistent. Some investigators have reported that opiate antagonists prevent or reverse the analgesic effects of exposure to noxious events [18,23] but others have reported little or no effect [5, 9, 16]. Similarly, there is a report of cross-tolerance between morphine and stress-induced analgesia [12], but the effect was quite small and appeared on only some behavioral measures. In addition, other investigators [6,8] have found no cross-tolerance at all between morphine and stress-induced analgesia. Nevertheless, the view has developed that perhaps exposure to noxious stimuli activates opiate systems, thus protecting the organism in some way.

Recently, Jackson and Maier [17,24] noted a relationship between stress-induced analgesia and a seemingly unrelated phenomenon, the learned helplessness effect. This term refers to the fact that organisms exposed to inescapable and unavoidable electric shocks in one situation frequently fail to learn to escape shock later in a different situation where escape is possible [25]. This phenomenon is of interest because it only follows inescapable and unavoidable shock, exposure to equivalent amounts of escapable shock does not produce a subsequent failure to learn. It is the uncontrollability of the shocks rather than shock *per se* which seems critical. Thus the determining factor here appears to be the psychologically interesting dimension of controllability rather than simple exposure to a painful event [24,25].

The stressors used in stress-induced analgesia studies have always been delivered so as to be nominally inescapable and unavoidable. This suggested that the inescapably shocked subjects in learned helplessness experiments might also be analgesic when later tested, and that this might be able to account for some of the effects of exposure to inescapable shock. Conversely, this raised the possibility that "coping factors" might be critical to stress-induced analgesia and the activation of opiate systems.

An obvious difficulty with this line of reasoning was that the learned helplessness effect is typically measured 24 hrs after inescapable shock exposure, but stress-induced analgesia often dissipates within 1–2 hrs after stress [1,5]. However, the behavioral techniques used to assess the learned helplessness effect involve reexposure to shock at the time of testing, while the procedures used in the stress-induced analgesia studies usually do not have this feature. This suggested the possibility that even though recovered in 2 hrs, the systems responsible for the analgesic response might remain in a sensitized state for at least 24 hrs, so that an analgesic reaction could be easily rearoused by reexposure to the stressor. Consistent with this possibility, Jackson and Maier [17,24] found that a brief exposure to shock insufficient to produce an analgesic reaction in control subjects did arouse an analgesic reaction on hot plate and tail-flick tests in subjects exposed to inescapable shock 24 hrs earlier. Further, this long-term analgesic reaction was specific to the uncontrollability of the original inescapable shocks—subjects first exposed to equal amounts of escapable shock did not become analgesic when reexposed to shock 24 hrs later.

These results suggest a number of questions. Perhaps the most obvious concerns whether endogenous opiates participate in the mediation of this long-term "helplessness analgesia." Investigation of endorphinergic involvement would provide information about a number of issues. It would comment on: (a) whether the long-term stress-induced analgesia which requires reexposure to the stressor for its expression reflects processes similar to or different from those involved in the short-term, stress-induced analgesias, (b) the potential involvement of opiates in the production of learned helplessness effects, and (c) the role of the psychological dimension of controllability in activating opiate systems.

The results of an initial series of experiments [23] investigating the effects of opiate antagonists are consistent with the notion of opiate mediation. The long-term analgesic reaction which follows inescapable shock was completely reversed by the opiate antagonists naltrexone and naloxone, whether administered before the inescapable shock session or the reexposure occurring 24 hr later. Although such reversibility by opiate antagonists is a necessary condition for implicating opiate involvement, it is not sufficient [27], primarily because the action of opiate antagonists are not completely specific to the opiate receptor. For example, naloxone has been reported to antagonize GABA [13].

A variety of other necessary conditions for opiate involvement have been suggested [27]. The most prominent is cross-tolerance with morphine. If some treatment activates opiate receptors, then it ought to be able to substitute for an opiate. Thus if tolerance to morphine has developed, tolerance to the effects of the other treatment should occur even though the subject has never before experienced that treatment.

The purpose of the experiment to be reported was to determine whether rats made tolerant to the analgesic effects of morphine by repeated morphine administration would also be tolerant to the analgesic effect which follows shock reexposure 24 hrs following inescapable shock treatment.

METHOD

Subjects

The subjects were 64 male albino rats obtained from the Holtzman Co., Madison, WI. The animals were from 90 to 100 days old at the start of the experiment. They were maintained on a 12-hr-light/12-hr-dark cycle, with food and water continuously available in the home cages.

Apparatus

Inescapable shocks or restraint occurred in Plexiglas restraining tubes which were 23.4 cm in length and 7.0 cm in diameter. The rat's tail extended from the rear of the tube and was taped to a Plexiglas rod. Unscrambled shocks were delivered by shock sources (modeled after the Grason-Stadler Model 700 shock source) through electrodes attached to the rat's tail with tape and augmented with electrode paste. The restraining tubes were located in separate sound attenuating chambers. Shock reexposure which took place immediately prior to analgesia testing was conducted in 4 two-way shuttleboxes. The shuttleboxes measured $34.5 \times 20.5 \times 19.5$ cm (L×W×D). Each chamber was divided into two equal sized compartments by a metal wall which spanned the width of the box from floor to ceiling. A rectangular opening 5.4 cm high and 5.5 cm wide was cut in the bottom of the wall which allowed rats to cross back and forth between compartments. The floors of the shuttlebox consisted of stainless-steel grids 0.35 cm in diameter and spaced 1 cm apart. Scrambled 0.6 mA shocks were delivered across grids to each shuttlebox by separate constant current shock sources.

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, 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.

Procedure

The rats were divided into 8 groups. The purpose of the first 4 groups was to determine whether the morphine regimen adopted would produce tolerance to the analgesic effects of morphine itself. Subjects from two of the groups (M-M; M-N) were given thirteen daily subcutaneous injections of 12.5 mg/kg morphine sulfate, while the subjects from the remaining two groups (S-M, S-S) received injections of an equivalent volume of saline. Daily administration of morphine for 13 days was chosen because stress-induced analgesia has been found to adapt or develop tolerance to itself following 13 daily exposures [22]. On the fourteenth day, 24 hr after their last injection, one of the morphine (M-M) and one of the saline (S-M) groups was given an injection of 12.5 mg/kg morphine sulfate followed by tail-flick testing 30 min later. The subjects from the remaining saline group (S-S) received a saline injection followed by tail-flick testing 30 min later. The remaining morphine group received only tail-flick testing on Day 14. A control saline injection was not used before testing in order to minimize conditioned analgesic effects. We wished to minimize such effects because the cross tolerance experiment (see below) does not include provision of injection cues before testing.

Each subject received three tail-flick testing trials. The interval between trials was spent in the rat's home cage and was approximately 3 min. On a test trial an experimenter who was unaware of group membership held the rat in his/her hand and placed the rat's tail in the grooved metal plate. A switch activated the heat lamp and a timer. The light beam was focused on a spot about halfway between the base and tip of the tail. The distance between the heat lamp and the tail was initially adjusted, using naive rats from the same shipment as those used in the study, to produce control group latencies in the vicinity of 8 sec. A trial was automatically terminated if a tail-flick did not occur within 20 sec and a 21 sec latency was recorded. This was necessary in order to prevent tissue damage.

The second set of 4 groups assessed cross tolerance between the analgesic effect of morphine and inescapable shock. On the first thirteen days, 2 groups (M-P, M-R) were given SC injections of 12.5 mg/kg morphine sulfate, while the remaining 2 groups (S-P, S-R) were given injections of an equivalent volume of saline.

The subjects were placed in the restraining tubes on day 14 of the experiment. Two of the groups (M-P, S-P) were given 80 5-sec 1.0 mA shocks through electrodes fixed directly to the tail. The shocks were delivered on a variable time 60 sec schedule (range of 5–200 sec). Subjects in Groups M-R and S-R were merely restrained in the tubes without shock for an amount of time equivalent to groups M-P and S-P. It should be noted that these shocking parameters and procedures are those used in learned helplessness experiments in Maier's laboratory. The use of identical procedures allows inferences to be made with regard to relationships between pain inhibition and learned helplessness. An escape-yoked procedure which compares escapably and inescapably shocked subjects was not used because prior work [17,24] has found that a long-term analgesic reaction does not follow escapable shock. Thus escapably shocked subjects would not reveal an analgesic reaction whose cross tolerance with morphine could be examined.

All subjects were given tail-flick analgesia tests 24 hr later. Tail flick testing was immediately preceded by 5 single-crossing shuttlebox escape/avoidance training trials. Five shuttlebox escape training trials were used to reexpose subjects to shock because that was the procedure previously used by [17, 23, 24]. These investigators used this procedure because they wished to make inferences concerning whether subjects might be analgesic during testing in their learned helplessness experiments. In these experiments learned helplessness was usually measured by the subjects performance in a shuttlebox escape task that required *2* crossings (FR-2) of the shuttlebox for shock termination. It is here that previously inescapably shocked subjects perform poorly. These FR-2 trials were always preceded by 5 single-crossing trials on which performance is usually unaffected. Thus measurement of the learned helplessness effect was preceded by 5 single crossing shuttlebox escape trials, and so the analgesia tests were preceded by this same treatment.

Shuttlebox trials were presented on a variable time 60 sec schedule (range of 5–200 sec). A 1000 Hz tone which raised the background noise level from 70 to 75 dB (re 0.0002 dynes/cm^2) was sounded at the beginning of each trial. If a response did not occur withn 5 sec of tone onset, a 0.6 mA scrambled shock was applied, and the tone and shock terminated whenever the rat crossed to the other side of the apparatus. A trial was automatically terminated if the subject did not respond within 35 sec of tone onset.

All subjects received 3 tail-flick tests following the completion of the 5 shuttlebox trials. The procedure used was identical with that already described, with the exception that the interval between trials was spent in the shuttlebox.

RESULTS AND DISCUSSION

Figure 1 shows the mean tail-flick latencies for the 4 groups that were designed to determine whether the morphine procedure used here is sufficient to produce tolerance to the analgesic effects of morphine. As can be seen, the administration of 12.5 mg/kg morphine produced a large analgesic reaction 30 min later in subjects not previously exposed to morphine (group S-M). Further, the administration of morphine for 13 days did not, by itself, produce a pronounced alteration of tail-flick responding 24 hr later (group M-N). Most importantly, rats which had received morphine for 13 days did show a reduced analgesic reaction to the morphine dose given on Day 14 (group M-M).

These impressions are confirmed statistically. An analysis of variance yielded a reliable treatment effect, $F(3,28)=33.85$, $p<0.001$. Neuman-Keuls comparisons ($\alpha=0.05$) indicated that groups S-S and M-N did not differ, and that both had significantly shorter tail-flick latencies than either groups S-M or M-M. In addition, group S-M latencies were reliably longer than those for group M-M.

Thus it is clear that 13 days of morphine administration at a 12.5 mg/kg dose is sufficient to produce a marked degree of tolerance to the analgesic effects of morphine given 24 hr later. Further, the amount of tolerance is quite substantial.

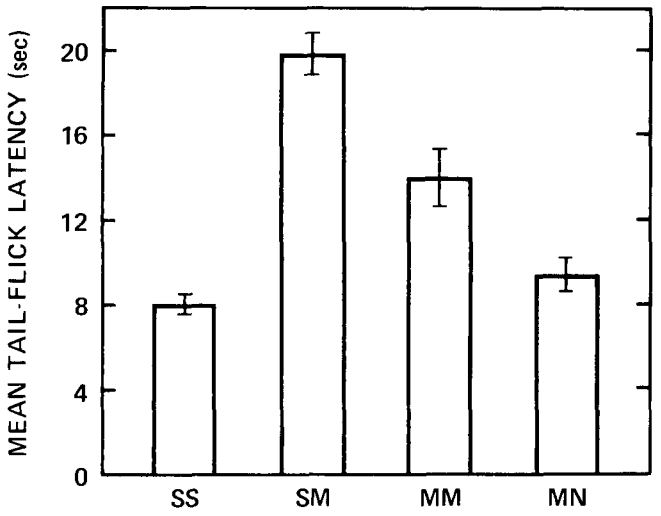

FIG. 1. Mean tail-flick latency for subjects given 13 days of saline or morphine followed by analgesia testing on Day 14.

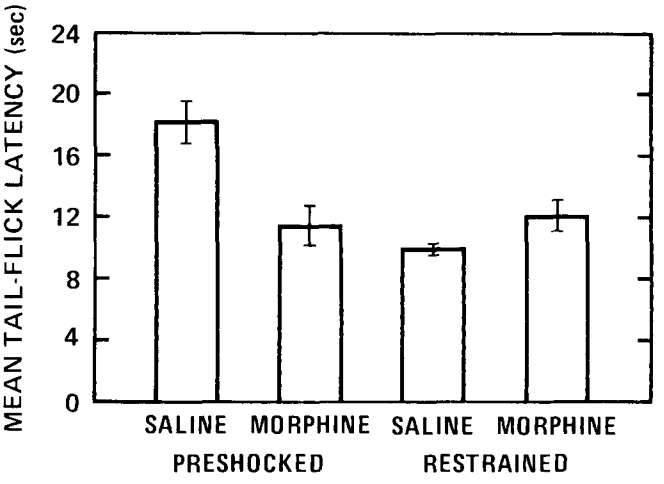

FIG. 2. Mean tail-flick latency for subjects given 13 days of saline or morphine, and then inescapable shock or restraint on Day 14.

The magnitude of tolerance obtained is more impressive when it is recognized that the latency scores for group S-M are an underestimate of the "true" group latency. This is because the tail-flick testing trials automatically terminated after 20 sec if no response had occurred. The fact that the mean latency for group S-M is almost 20 sec indicates that these subjects failed to respond on most trials.

Although the logic of the experiment does not require tolerance to be complete, it should be noted that complete tolerance was not obtained. However, whether tolerance to morphine is complete is as likely to be determined by the test dosage as it is by the tolerance regimen. In the present experiment, a relatively high dose (12.5 mg/kg) was used as the test dose. Further, this dose was the same as that used for daily administration. This procedure mitigates against finding complete tolerance. Studies which find complete tolerance often use test dosages that are small in absolute terms and also much smaller than those used for the daily injections [8].

These data make it reasonable to examine whether cross tolerance develops between the morphine treatment used here and the long-term analgesic effects of inescapable shock. Recall that the 4 groups designed to assess such cross tolerance were given 5 trials of shuttlebox shock escape before tail-flick testing. Latencies to perform single-crossing escape responses in the shuttle-box did not differ among groups, $F(3,28)<1.0$. They were not affected by prior exposure to inescapable shock, $F(1,28)<1.0$, and prior exposure to morphine also had no impact on FR-1 escape latencies, $F(1,28)=1.030$, $p>0.25$. The mean escape latencies for the 4 groups were 6.3, 5.3, 4.8, and 4.7 sec for groups S-P, S-R, M-P, and M-R respectively.

Figure 2 shows the mean tail-flick latencies for the various groups. As can be seen, the usual analgesic effect of inescapable shock was observed (Group S-P vs S-R). Chronic morphine administration *per se* did not have a substantial effect on tail-flick latencies (Group M-R vs S-R). Most importantly, the chronic administration of morphine prior to the inescapable shock session reduced or eliminated the analgesic response that would otherwise have appeared 24 hr later following reexposure to shock (Group M-P vs S-P).

These impressions are confirmed statistically. A factorial analysis of variance revealed a reliable effect of inescapable shock treatment, $F(1,28)=12.82$ $p<0.005$, a marginally reliable effect of chronic morphine administration, $F(1,28)=3.42$ $p=0.0717$, and a reliable interaction between inescapable shock and chronic morphine administration, $F(1,28)=14.08$ $p<0.001$. Neuman-Keuls tests revealed that group S-P differed reliably from all the others ($p<0.05$), which did not differ among themselves.

Thus, subjects that had received a session of inescapable shock following 13 days of chronic morphine administration did not exhibit the typical long-term analgesic response induced by inescapable shock. The fact that morphine is cross-tolerant with β-endorphin [30] suggests that the common element is likely to involve endogenous opiate peptides. The complete reversal of the long-term helplessness analgesia by opiate antagonists is consistent with this possibility.

It should be noted that the data, by themselves, indicate only that 13 days of morphine treatment prevents inescapable shock delivered 24 hr later from having an analgesic effect. It is inferred that tolerance to morphine is the critical feature, but this need not be true. Two possibilities require comment. One is that 13 days of morphine results in a reduced pain sensitivity of Day 14, thus reducing the painfulness of the shocks administered on Day 14. This might mitigate against the shocks' analgesic consequences. Such an alternative is made unlikely by the data from the first set of 4 groups. Group M-N was given 13 days of morphine and then tested for pain sensitivity on Day 14. No shift in pain reactivity occurred. Moreover, group M-R received 13 days of morphine and testing on Day 15, and also failed to reveal a change in tail-flick responding. Thus there is no evidence for a decrease in pain sensitivity/reactivity 24 or 48 hr following the chronic morphine procedure used here.

The second possibility is that opiate withdrawal might have been occurring during the Day 14 inescapable shock procedure, and that some symptom of withdrawal might

have interacted with the inescapable shock to prevent it from having an effect. There are two difficulties with this proposal. It is not clear how a symptom of withdrawal would prevent inescapable shock from exerting its usual impact. Opiate withdrawal is characterized by increased rather than decreased irritibility, and this would seem likely to magnify rather than reduce the effects of shock.

Moreover, the present data do not reveal the occurrence of withdrawal symptoms at the time during which the shock session occurs. Group M-S was tested 24 hr after the last morphine injection and did not evidence the reduction in tail-flick latencies that would be expected as a product of withdrawal.

Finally, other studies called "cross tolerance" have these same features, and the assumption has been made that tolerance is the crucial factor. Thus we will continue to refer to the present finding as cross tolerance.

The complete cross-tolerance with morphine found here contrasts with the complete lack of cross-tolerance reported by others who have used different stress-induced analgesia methodologies [6,9]. Bodnar *et al.* employed a 3.5 min swim in 2°C water as the stress procedure and assessed nociceptive responding 30 min later, while Chance and Rosecrans utilized exposure to 15 sec of shock or exposure to the originally neutral cues present during the 15 sec shock session and measured pain responsivity 15 sec later. Analgesic reactions were not diminished in morphine-tolerant subjects. There are at least 3 possible explanations for the discrepancy between the present results and those of Bodnar *et al.* and Chance and Rosecrans. The most obvious is that the various studies may have used different morphine regimens, and some may be more likely to produce cross-tolerance than others. However, the actual procedures used do not encourage this possibility. Bodnar *et al.* employed 14 daily doses of 10 mg/kg, Chance and Rosecrans gave 10 daily doses increasing from 10 mg/kg to 60 mg/kg and continued with 60 mg/kg doses during the 6 days of testing, and we employed 13 daily doses of 12.5 mg/kg. Thus our dosage was very similar to that used by Bodnar *et al.*, and much lower than that used by Chance and Rosecrans.

A second more interesting possibility is that short-term and long-term analgesic reactions may be mediated by different processes, with opiate involvement being restricted to long-term effects. The complete reversibility of the long-term effect by opiate antagonists [23] and the lack of influence of opiate antagonists on other short-term effects [5, 8, 16] is consistent with this possibility. Interestingly, naloxone has either no effect or only a small effect on the analgesic reaction produced by the very same procedures just described which show no cross-tolerance with morphine [5,8].

However, there is a third possibility which is also consistent with our results and the available literature. The parameters of noxious stimulation, rather than the testing interval, may critically determine the sort of process activated. Thus the important difference between studies may not be short-term testing without reexposure versus long-term testing with reexposure, but rather 3-5 min of cold swim and 15 sec of electric shock versus 80 5-sec shocks occurring across a 90 min interval. In fact, Lewis, Cannon, and Liebeskind [18] have recently made just such a suggestion. They found that both a 3-min exposure to continuous shock and a 30-min exposure to intermittent shock produced an immediately following antinociceptive reaction. However, only the analgesic reaction induced by the 30-min exposure to shock was reversed by naloxone. This led Lewis *et al.* [18] to suggest that only prolonged exposure to a stressor activates opiate processes. A brief exposure to a stressor was argued to produce pain inhibition via nonopiate mechanisms. Consistent with this argument, Maier *et al.* [23] found that even the short-term analgesia which follows exposure to their inescapable shock procedures could be completely blocked by opiate antagonists. Thus the differing cross-tolerance results may be caused by the differing treatment conditions used. In support of this notion, cross tolerance with morphine has been reported to follow prolonged but not brief shock sessions [19]. Contrary to the suggestion that opiate processes are not involved in the mediation of stress-induced analgesia [5], opiate processes may be critical, but only if the stress conditions meet certain requirements, such as an extended duration. It should be noted that this may be so, even if it is not the tolerance induced by the chronic morphine regimen that is critical.

It has been argued that the organism's learning that it has no control over the aversive stimulus is critical to the production of the learned helplessness effect. This sort of learning might well require extensive exposure to the inescapable and unavoidable aversive stimuli, and it is possible that it is such learning that activates opiate systems. Thus duration *per se* may not be critical, but longer durations of exposure may simply increase the probability that the organism learns that the inescapable and unavoidable events are inescapable and unavoidable. Alternatively, the amount of stress may be critical with duration affecting amount of stress. We cannot separate these possibilities at the present time. Nevertheless, it is clear that the analgesic reaction that follows shock conditions that produce both learned helplessness effects and analgesia 24 hrs later is reversed by opiate antagonists [23] and is cross-tolerant with morphine. This suggests a role for the endogenous opiates in learned helplessness and a role for the psychological dimension of control in activating opiate systems.

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