Physiology & Behavior, Vol. 30, pp. 731–734. Pergamon Press Ltd., 1983. Printed in the U.S.A.

Opiate Antagonists Overcome the Learned Helplessness Effect but Impair Competent Escape Performance

WAYNE G. WHITEHOUSE, JOSEPH WALKER,
DAVID L. MARGULES AND PHILIP J. BERSH

Department of Psychology, Temple University, Philadelphia, PA 19122

Received 7 January 1983

WHITEHOUSE, W. G., J. WALKER, D. L. MARGULES AND P. J. BERSH. *Opiate antagonists overcome the learned helplessness effect but impair competent escape performance.* PHYSIOL BEHAV 30(5)731–734, 1983.—Rats exposed to inescapable shocks exhibited deficiencies in learning to escape shock in a novel situation 24 hours later (learned helplessness). Opiate antagonists (naloxone or naltrexone) blocked the learned helplessness effect, allowing efficient escape performance on the subsequent test. In contrast, these drugs impaired the performance of rats pretrained with escapable shocks and animals with no previous exposure to shock. Both effects occurred at small doses and increased substantially with higher doses. The results suggest a significant role for endogenous opiates in the induction of learned helplessness as well as in the acquisition of efficient escape behavior.

Analgesia Endogenous opioids Learned helplessness Opiate antagonists Rats

CONTROLLABILITY of aversive events has been shown to be an important variable affecting the future adaptive functioning of organisms. Exposure to inescapable (uncontrollable) shocks in one situation may significantly retard acquisition of escape behavior in a novel situation 24 hours later. Escape deficits of this nature are not observed in organisms which were previously exposed to identical, but escapable (controllable), shocks, nor in non-preshocked organisms. This interference effect produced by prior exposure to inescapable shocks may result from the organism's sensitivity to the ineffectiveness of its behavior—the so-called learned helplessness effect [9]. Accordingly, the learning of independence between behavior and shocks during pretreatment could produce a kind of passivity that generalizes to subsequent situations involving shock, thereby impairing later performance. One line of evidence favorable to the learned helplessness hypothesis is that forced exposure of the "helpless" organism to the reinforcement contingencies of the test situation restores escape performance to control levels [10, 11, 12].

The endogenous opioid peptides provide a potential physiological basis for the learned helplessness effect. Morphine and related opioids can produce passivity of behavior [1]. Interestingly, rats receiving inescapable tailshock subsequently exhibit reduced nociceptive reactivity on tail-flick and hot plate analgesimetric tests which does not occur following escapable tailshock or simple restraint [5]. Moreover, although the analgesic reaction induced by inescapable shock is of a relatively transient nature, it can be restored 24 hours later by brief reexposure to shock [5], a common feature of the typical escape acquisition test for helplessness effects. Maier and his associates [8] found that the opiate antagonist, naltrexone, successfully blocked both the short- and long-term analgesic reactions induced by exposure to inescapable shocks, suggesting that endogenous opiate systems may subserve these effects.

The present experiment investigated whether opiate antagonists might also block the usual interference with shuttlebox escape learning produced by prior inescapable shocks. This effect of opiate antagonists would be anticipated if inescapable-shock-induced analgesia mediated the shock-escape deficits observed in the shuttlebox.

METHOD

Subjects

The subjects were 84 male rats of Long-Evans descent, weighing between 230–280 g at the start of the experiment. Animals were housed individually and permitted ad lib access to food and water.

Apparatus

Pretraining was carried out in three identical operant chambers, with the dimensions 30.2×24.0×36.8 cm (L×W×H). Sidewalls and ceilings were constructed of clear Plexiglas, while the front and rear walls were made of stainless steel. A stainless steel lever protruded 2.5 cm into each chamber from the left corner of the front wall, and required a force of 10 g (0.1 N) to depress. The floor of each chamber consisted of stainless steel grids, 0.5 cm in diameter and spaced 1.8 cm apart (center-to-center). In two of the chambers, 1.0 mA constant-current shocks were applied periodically to the grid floor by separate Coulbourn Instruments

E13-16 solid state shocker/distributors. No shocks were delivered in the third chamber. All chambers were enclosed in individual sound-attenuating cubicles.

Escape testing was administered in a 19.0-cm wide × 22.5-cm high × 46.0-cm long two-way shuttlebox, with Plexiglas sidewalls and ceiling and stainless steel end walls. The shuttlebox was housed in a sound-attenuating enclosure, and was divided in half by a stainless steel partition with a 6.0×7.0 cm rounded archway cut out of it. Each shuttlebox compartment had 10 stainless steel grids, 0.5 cm in diameter and spaced 0.95 cm apart, serving as the floor through which shocks of 1.0-mA intensity, provided by a Coulbourn E13-16 shocker, could be delivered. Crossings, by the subject, from one compartment to the other, were detected by microswitches in contact with the tilt floor.

Procedure

The experimental design was a 3×3 factorial, involving three levels of shock pretraining (i.e., escapable shock (ES), inescapable shock (IS), and no shock (NS)) crossed with three levels of drug (i e., saline, 1.0 mg/kg naltrexone, and 10.0 mg/kg naltrexone). Four triads, consisting of animals exposed to the ES, IS, and NS pretraining conditions, were also tested in the shuttlebox following subcutaneous administration of 10 mg/kg naloxone hydrochloride. Since their results were comparable, in all respects, to their naltrexone-treated counterparts, only the procedure and results of the latter group will be described.

During the pretraining phase, 72 rats were unsystematically assigned to triads. Two members of each triad were yoked to receive shocks of identical physical characteristics; the third member, NS was not shocked during this phase. Of the yoked partners, animals designated as ES could terminate shock, after a minimum duration of 1 sec, by making a lever-press response. Animals designated as IS could also press the response lever, but such behavior had no effect upon shock; shock termination for the IS animal was entirely contingent upon the behavior of the ES animal and shock was thus inescapable. Shocks were programmed to occur on a variable-time 60 sec schedule, and, in the absence of a response by the ES rat, terminated automatically after 30 sec. Pretraining continued for approximately 90 min until 80 shock trials were delivered.

The test phase was conducted 24 hours later. At this time, eight triads were randomly selected to receive subcutaneous injections of either saline (0.9% NaCl), 1 mg/kg naltrexone hydrochloride, or 10 mg/kg naltrexone hydrochloride, 15 min prior to the shuttlebox escape acquisition test. The test consisted of 35 shock-escape trials, separated by a variable intertrial interval (mean=60 sec; range=10–120 sec). Escape from shock for the first five trials occurred when the animal crossed from one compartment to the other (FR 1). For all trials after this, shock termination was contingent upon the animal's crossing from one compartment to the other and then returning to the original compartment (FR 2). Failure to meet the response requirement on any trial resulted in a full 60 sec of shock.

RESULTS

All animals in the ES pretraining condition rapidly acquired the lever-press escape response and escaped shock on each of the 80 pretraining trials. This is important since any acquisition failures during pretraining would jeopardize the inference that subsequent differences in shuttlebox performance were due to differences in prior controllability of shock. Pretraining escape latencies for ES animals were statistically equivalent, $F(2,21)=2.49$, $p>0.10$ across dose treatments (means=4.19, 3.04, and 5.39 sec per trial for saline, 1 mg/kg, and 10 mg/kg groups, respectively), thereby ensuring comparable shock exposure for all groups during pretraining.

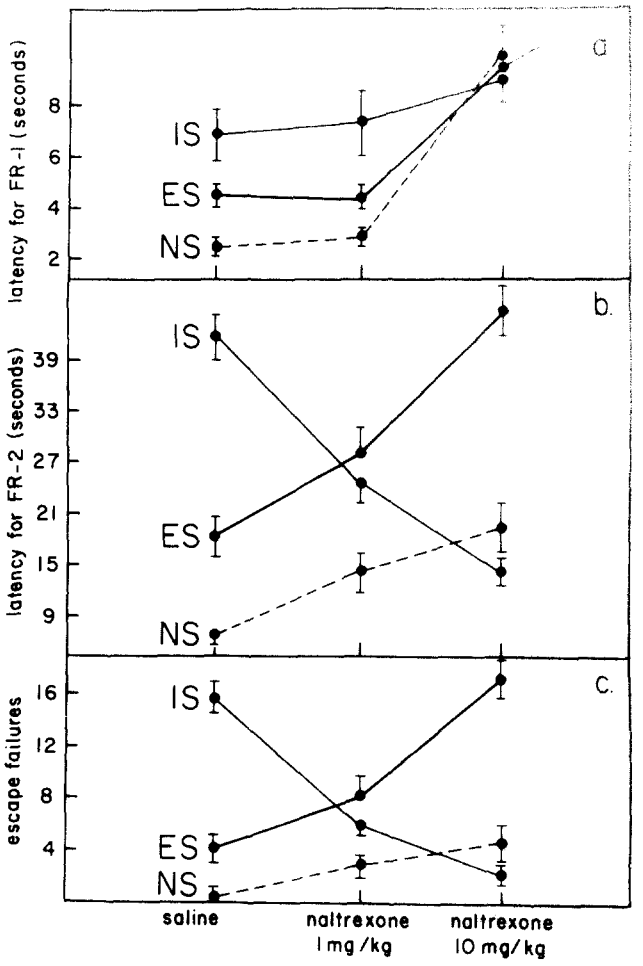

FIG. 1. (a) Mean latency to escape shock during the initial 5 trials (FR 1) of the shuttlebox acquisition test. (b) Mean latency to escape shock during the subsequent 30 trials (FR 2) of the shuttlebox acquisition test. (c) Mean failures to escape shock out of 35 trials of the shuttlebox acquisition test. Vertical lines indicate standard errors of the mean.

Shuttlebox performance was analyzed separately for three dependent variables: FR 1 escape latency, FR 2 escape latency, and number of escape failures. Summary measures on these variables are depicted graphically in Fig. 1 as a function of dose treatment. As is usual in shuttlebox escape tests for helplessness effects, FR 1 escape latencies were unaffected by prior exposure to either escapable, inescapable, or no shock [7]. The main effect of drug dose was statistically significant, $F(2,63)=7.35$, $p<0.01$. Newman-Keuls post hoc tests ($p<0.05$) indicated that 10 mg/kg naltrexone significantly elevated FR 1 escape latencies for ES and NS groups, but not for the IS group, relative to their 1 mg/kg naltrexone and saline counterparts (Fig. 1a). FR 1 perform-

ance was comparable for all groups, across the controllability factor, under saline and 1 mg/kg naltrexone.

A factorial analysis of variance (ANOVA) performed on the FR 2 latency data yielded significant main effects for both shock pretreatment, $F(2,423)=58.66$, $p<0.001$ and drug dose, $F(2,423)=4.36$, $p<0.05$ factors, as well as a significant interaction between them, $F(4,423)=45.93$, $p<0.001$ (see Fig. 1b). Interference effects, resulting from prior exposure to inescapable shocks, usually become substantial when two crossings of the shuttlebox (FR 2) are required for escape [7]. This was confirmed in the present experiment by Newman-Keuls comparisons ($p<0.05$) which indicated that, for animals given subcutaneous saline injection prior to testing, Group IS was significantly retarded in escaping shock relative to Groups ES and NS, while Group ES was also slower to escape shock than Group NS (Fig. 1b). Although a latency difference between the ES and NS group is not a typical result [9], neither is it damaging to any current theory of the helplessness phenomenon. Of primary concern here is the effect of naltrexone administration upon FR 2 escape latencies. As indicated in Fig. 1b, a 1 mg/kg dose of naltrexone significantly reduced escape latencies for the IS group as compared to the IS group given saline. The same dose administered to ES rats, however, actually resulted in a reliable increase in escape latencies relative to saline control levels, and the same was true for NS rats. Newman-Keuls tests revealed that Group NS exhibited reliably shorter escape latencies than either Group ES or IS, which did not differ from each other. The most dramatic effects were obtained with the 10 mg/kg dose. At this dose, interference with escape behavior in the IS group was virtually eliminated, with latencies being statistically equivalent to those of the NS group. On the other hand, ES animals which received 10 mg/kg naltrexone prior to the shuttlebox test showed escape latencies of the same magnitude as IS animals in the saline condition. The performance of NS rats was also impaired, but only to the level observed in their counterparts given 1 mg/kg naltrexone. Thus, with a dose of 10 mg/kg, naltrexone completely reversed the effects of prior shock controllability upon later shuttlebox escape performance.

Figure 1c shows the mean number of failures to escape shock for each group during the shuttlebox escape test. A factorial ANOVA indicated that the shock pretreatment factor, $F(2,63)=9.42$, $p<0.001$ and the pretreatment $\times$ dose interaction, $F(4,63)=10.12$, $p<0.001$) were significant. Newman-Keuls comparisons indicated that the frequency of escape failures was significantly greater for IS-saline animals and ES-10 mg/kg naltrexone animals than for any other groups. No reliable differences existed among these latter groups, nor did IS-saline and ES-10 mg/kg naltrexone differ from each other.

DISCUSSION

These results indicate that exposure to inescapable shocks, of the parameters used here, produced substantial interference with shuttlebox escape learning 24 hours later. Exposure to identical, but escapable, shocks retarded FR 2 escape latencies relative to non-preshocked rats, but did not impair shuttlebox performance to anywhere near the level of interference resulting from prior exposure to inescapable shocks. The interference effect of inescapable shocks upon subsequent shuttlebox escape acquisition may well be mediated by an increase in the activity of an endogenous opioid substrate, as suggested by recent work on stress analgesia [4, 6, 8]. Thus, reductions in shuttle escape interference following exposure to inescapable shocks were significantly related to dose levels of the opiate antagonists, naloxone and naltrexone. At the highest dose of naltrexone (10 mg/kg), for example, seven out of eight inescapably shocked rats escaped efficiently on each of the shuttlebox test trials, while the one animal which performed poorly failed to escape on only eight of 35 trials. This pattern of results is entirely consistent with an opioid interpretation of the learned helplessness phenomenon. According to this view, exposure to inescapable shocks induces a short-term opioid reaction. The opioid condition is reinstated by reexposure to shock 24 hours later [5] and may therefore reduce nociceptive reactivity and/or reduce motor activity [1] during shuttlebox shock escape testing, resulting in impaired escape performance. Naltrexone administered prior to inescapable shocks or prior to brief reexposure to shock reverses the analgesic response otherwise observed [4,8], suggesting a role for some endogenous opiates in mediating the analgesia induced by exposure to inescapable shocks. Similarly, the present study found that naltrexone effectively reduces shuttlebox escape interference resulting from prior inescapable shocks, and, in high concentrations, virtually eliminates it.

In the present experiment, administration of opiate antagonists led to dose-dependent increases in shuttlebox escape interference by rats pre-exposed to escapable shocks. In addition, even non-preshocked animals exhibited a tendency for these drugs to impair escape learning, although the level of interference was not increased by larger doses. Perhaps the effect of administering opiate antagonists is to reduce opioid activity below normal levels for these groups. The resultant hyperalgesic condition [2], could, in turn, cause a deterioration of shuttlebox performance, due, possibly, to the tendency for the now "subjectively more painful" shocks to evoke a variety of unconditioned, potentially antagonistic responses or strong emotional reactions [3].

At this stage, however, the role of endogenous opioids in modulating the effects of exposure to controllable and uncontrollable aversive events is far from clear. Nor do the obvious parallels between the present results and those pertaining to stress-induced analgesia [4, 5, 6, 8] require that a single opiate effect mediate the two phenomena. Nevertheless, the finding that opiate antagonists interact strongly with pretraining controllability to influence subsequent escape performance corroborates other results [4,8] which suggest that "psychological" factors may be particularly important determinants of whether, and the extent to which, endogenous opiate systems become involved in the management of acute stress.

ACKNOWLEDGEMENTS

This research was supported in part by a Biomedical Research Support Grant from Temple University to W. G. Whitehouse, by grant #BNS-7920616 from the National Science Foundation to D. L. Margules, and in part by a Grant-in-Aid of Research from Temple University to P. J. Bersh. We are grateful for the able technical assistance of A. Maliniak, S. McGarvey, and E. Whitehouse.

REFERENCES

1. Berger, P. A., H. Akil, S. J. Watson and J. D. Barchas. Behavioral pharmacology of the endorphins. In: *Annual Review of Medicine*, edited by W. P. Creger, C. H. Coggins and E. W. Hancock. Palo Alto, CA: Annual Reviews, 1982, pp. 397–415.
2. Carmody, J. J., P. R. Carroll and D. Morgans. Naloxone increases pain perception in rats and mice. *Life Sci* **24:** 1149–1152, 1979.
3. Fanselow, M. S. and R. C. Bolles. Naloxone and shock-elicited freezing in the rat. *J Comp Physiol Psychol* **93:** 736–744, 1979.
4. Grau, J. W., R. L. Hyson, S. F. Maier, J. Madden IV and J. D. Barchas. Long-term stress-induced analgesia and activation of the opiate system. *Science* **213:** 1409–1411, 1981.
5. Jackson, R. L., S. F. Maier and D. J. Coon. Long-term analgesic effects of inescapable shock and learned helplessness. *Science* **206:** 91–93, 1979.
6. Lewis, J. W., J. T. Cannon and J. C. Liebeskind. Opioid and nonopioid mechanisms of stress analgesia. *Science* **208:** 623–625, 1980.
7. Maier, S. F., R. W. Albin and T. Testa. Failure to learn to escape in rats previously exposed to inescapable shock depends on nature of escape response. *J Comp Physiol Psychol* **85:** 581–592, 1973.
8. Maier, S. F., S. Davies, J. W. Grau, R. L. Jackson, D. H. Morrison, T. Moye, J. Madden IV and J. D. Barchas. Opiate antagonists and long-term analgesic reaction induced by inescapable shock in rats. *J Comp Physiol Psychol* **94:** 1172–1183, 1980.
9. Maier, S. F. and M. E. P. Seligman. Learned helplessness: Theory and evidence *J Exp Psychol (Gen)* **105:** 3–46, 1976.
10. Seligman, M. E. P., S. F. Maier and J. Geer. The alleviation of learned helplessness in the dog. *J Abnorm Soc Psychol* **73:** 256–262, 1968.
11. Seligman, M. E. P., R. A. Rosellini and M. J. Kozak. Learned helplessness in the rat: Reversibility, time course, and immunization. *J Comp Physiol Psychol* **88:** 542–547, 1975.
12. Williams, J. L. and S. F. Maier. Transituational immunization and therapy of learned helplessness in the rat. *J Exp Psychol (Anim Behav)* **3:** 240–253, 1977.