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The Effect of Morphine on Pain-Elicited Aggression in Rats

Danija Kaskurs
Western Michigan University

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THE EFFECT OF MORPHINE ON PAIN-ELICITED AGGRESSION IN RATS

by

Dagnija Kaskurs

A Thesis submitted to the Faculty of the School of Graduate Studies in partial fulfillment of the Degree of Master of Arts

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Dagnija Kaskurs
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INTRODUCTION

Experimental work on drug addiction has increased in recent years. Numerous studies (reviewed by Martin, Wikler and Eades, 1963) have investigated the phenomena of dependence, tolerance and withdrawal in animals. Other experiments have been concerned with the development of purposive drug-seeking behavior in animals comparable to that of human addicts (Beach, 1957a; Nichols, 1963; Weeks, 1964). No specific experimental work has been reported on the effect of morphine on aggression, although the clinical and anecdotal data indicate that morphine reduces aggression in human addicts (Kolb, 1925; Nyswander, 1959; Cameron, 1963). The present experiment is concerned with the effect of morphine on shock-elicited aggression in rats.

A somewhat related experiment (Tedeschi, Tedeschi, Mucha, Cook, Mattis, and Fellows, 1959) was designed to investigate the effects of various centrally-acting drugs on pain-elicited aggression in mice. One of the drugs, meprobamate, showed a particular profile of activity, which included a mild depression of spontaneous activity and a more pronounced suppression of fighting. Other compounds also suppressed fighting, but only when marked motor inactivation was produced. The decrease
in fighting in those cases was probably due to the gen-
eral depressive effects of the drugs rather than to any
specific action on aggression. On the basis of a num-
ber of studies, Martin et al. (1963) have concluded
that low doses of morphine (up to 30 mg./kg.) generally
produce excitant effects and that higher doses produce
depressant effects, to which tolerance is quickly de-
veloped. Collins (1965) has noted that the depressant
effect of morphine becomes more pronounced after loss
of body-weight, and concludes that any decrease in acti-
vity may be related to decrease in hunger drive, and
that both may be traced to general drive reduction,
rather than to any specific effect of morphine on motor
activity.

Numerous studies on aggression have shown that
fighting in response to aversive environmental stimu-
lation appears to be a hereditarily determined segment
of behavior and not attributable to any form of pre-
vious conditioning (Ulrich, Hutchinson and Azrin, 1965).
For the purposes of this study pain-elicited aggression
provides a readily identifiable and easily measurable
form of unconditioned aggression to serve as the depen-
dent variable. The relation of numerous shock parame-
ters and environmental conditions to the probability of
occurrence of aggression in response to electric foot
shock has been well documented (Ulrich and Azrin, 1962). Relevant variables noted by Ulrich and Azrin include shock intensity, frequency, duration, and consistency, as well as other factors such as amount of floor space and orientation of the animals. Fighting behavior has been shown to occur most reliably at shock intensities of 2-3 ma. With increased shock frequency probability of aggression also increases, up to the point where shock is made so frequent as to be almost continuous. Longer shock duration tends to increase the probability of fighting up to the point at which it becomes physically debilitating. Failure to use a shock scrambler results in inconsistent fighting as the animals are able to escape the shock. Floor space is a critical factor in that use of a large chamber increases the possibility of accidental variables such as position and orientation at the time of shock presentation affecting the rate of aggression.

On the basis of these data, shock parameters were selected to produce a reliable, moderate rate of fighting prior to the introduction of the drug so that any decrease and/or increase could be adequately recorded.

Morphine injections were started at the rate of 9 mg./kg./day and increased up to 45 mg./kg./day. A similar schedule has been suggested by Nichols (1963).
He has noted that injections of 40 mg./kg. daily for two weeks are capable of substantially increasing opiate-seeking behavior. Beach (1957a) has shown that doses of as little as 5 mg./kg. can produce morphine-seeking behavior. While, in the present study, the aim does not include demonstration of addiction, it was felt that the above doses would ensure the development of tolerance and physical dependence to the drug.
METHOD

Subjects. Subjects were ten male albino rats, approximately ninety days old and weighing between 240 and 276 grams at the beginning of the experiment. Rats were individually caged and food and water were available at all times in the home cages.

Apparatus. The experimental compartment measured twelve inches by seven inches by seven inches and was located inside a sound attenuated chest, the floor of which was constructed of parallel bars through which the shock was delivered. The chamber was situated against the back wall of the chest. Two clear plastic sides and plexiglas door permitted unrestricted observation. Illumination was provided by two ten-watt bulbs located near the top back corners of the chest. The stimulus conditions used in the experiment were programmed by a system of relay circuitry and related timers in a separate room. Fighting responses were recorded on counters by the experimenter with a microswitch at the experimental chamber. A shock scrambler ensured a changing pattern of polarities, so that any two adjacent grids would be of opposite polarity during a major part of each shock presentation. During experimental
sessions the door of the room and the door of the chest were kept closed to eliminate background stimulation.
A clear view of the experimental chamber was provided by a window in the door of the chest opposite the chamber.

**Procedure.** Subjects were divided into pairs and assigned to experimental and control groups. There were three pairs in the experimental group and two pairs in the control group. The experiment consisted of three parts: aggression baseline, morphine habituation and withdrawal of the drug. Aggression trials were conducted in the same way for all parts of the experiment. Each pair of rats was placed in the experimental chamber and electric foot shock was presented. The number of aggressive responses was recorded by the experimenter. An aggressive response was defined as "any striking or biting movement of either or both animals toward the other" (Ulrich and Azrin). This usually occurred in the stereotyped fighting position (i.e. facing each other in an upright position), but striking and/or biting were taken as the decisive variables.

**Aggression baseline.** Baseline trials were conducted for eighteen days, to establish the aggressive response and to determine the frequency of its occurrence for each pair prior to the introduction of the experimental
variable. Each session lasted fifteen minutes, with four shocks per minute, making a total of sixty shocks per pair per session. For the first nine days, shock intensity was 1.6 ma. and shock duration was 0.5 seconds. These parameters were selected to give approximately 50 percent fighting responses, so that both increases and decreases in fighting could be seen when the experimental variable was introduced. It has been found that at shock intensities below 2 ma. fighting tends to be unstable (Ulrich and Azrin, 1962), and this was observed over the first nine sessions. While increasing the shock intensity would have ensured greater stability in aggression, it would also have raised the rate of aggression well above the desired 50 percent level. It was, therefore, decided to increase shock duration to 0.75 seconds for the rest of the experiment and to keep shock intensity at 1.6 ma. Baseline trials were conducted for another six days using these parameters and a fairly stable medium rate of aggression was obtained for all pairs.

Morphine habituation. Experimental animals received sub-cutaneous injections of morphine twenty minutes prior to each session for thirteen days. The amount and sequence of injections are presented in Table I. Control animals were injected with a corresponding
volume of sterile water. Aggression trials were conducted in the same way as in the baseline sessions.

TABLE I

Drug dosage during habituation

(All rats weighed approximately one-third kilogram when injections were begun, and that weight was assumed in calculating absolute dosage. Although weight fluctuations did occur during habituation, it was considered more desirable to give equal doses to all animals rather than add more variables to the experiment by adjusting dosage for each animal according to its weight each day.)

<table>
<thead>
<tr>
<th>Days</th>
<th>Dosage</th>
<th>Absolute Dose</th>
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<tbody>
<tr>
<td>1-5</td>
<td>9 mg./kg.</td>
<td>3 mg.</td>
</tr>
<tr>
<td>6</td>
<td>15 mg./kg.</td>
<td>5 mg.</td>
</tr>
<tr>
<td>7</td>
<td>21 mg./kg.</td>
<td>7 mg.</td>
</tr>
<tr>
<td>8</td>
<td>24 mg./kg.</td>
<td>8 mg.</td>
</tr>
<tr>
<td>9</td>
<td>36 mg./kg.</td>
<td>12 mg.</td>
</tr>
<tr>
<td>10-13</td>
<td>45 mg./kg.</td>
<td>15 mg.</td>
</tr>
</tbody>
</table>

Drug withdrawal. Experimental sessions were continued for ten days after injections of the drug were stopped.
RESULTS

Figures 1 through 5 show the percentage of aggressive responses to shock for each pair of rats each day. Figures 1 through 3 show the results for the experimental rats, and Figures 4 and 5 show the results for the control rats. Figure 6 indicates the mean number of aggressive responses for each pair in the three different experimental parts.

Baseline. Individual differences in rate of aggression are noticeable during the first four sessions. After that, fighting responses become more stable, except for fluctuations which occurred while shock parameters were being adjusted. In the last six baseline sessions aggressive responses for all pairs are more uniform, and range between forty and sixty percent aggression.

Morphine habituation. Fighting in all three experimental pairs decreased markedly upon introduction of the drug. Some increase was noted when the drug was held constant at 9 mg./kg., but as dosage was increased, fighting decreased again and was completely absent when the first dose of 45 mg./kg. was administered.

Control animals continued to show a rate of aggression similar to that shown in baseline sessions.
At this stage of the experiment one of the control animals (rat #4) died and was replaced by a naive rat, but there was no marked change in the fighting behavior of that pair.

**Withdrawal.** Upon withdrawal of the drug, fighting in experimental pairs increased sharply, reaching a peak on the second day off the drug. Due to the death of rats #2 and #5, rats #1 and #6 were paired after the first day of withdrawal, but this did not appear to affect the rate of aggression which was similar to that shown by the other surviving pair. Fighting decreased after the second day, but, at the conclusion of the experiment, was still slightly more frequent than during the baseline sessions.

Figures 4 and 5 show fluctuations in fighting by the control animals throughout the experiment, but none of these are systematic, and the same basic pattern is retained.

Figure 6 summarizes the data by showing the mean percentage of aggressive responses made by each pair under the three different experimental conditions. It indicates clearly the sharp decrease in aggression by the drug animals during habituation and the sharp increase upon withdrawal of the drug. This is compared to the comparatively slight changes in rate of aggression by the control animals.
Fig. I. The percentage of aggressive responses to shock each session. Rats 1 and 2 (experimental).
Fig. 2. The percentage of aggressive responses to shock each session, Rats 5 and 6 (experimental).
Fig. 3. The percentage of aggressive responses to shock each session.
Rats 9 and 10 (experimental).
Fig. 4. The percentage of aggressive responses to shock each session.
Rats 3 and 4 (control).
Fig. 5. The percentage of aggressive responses to shock each session.
Rats 7 and 8 (control).
Fig. 6. Mean percentage of aggressive responses.
Weight. Records of the animals' weight were kept throughout the experiment to indicate some of the physical effect of the drug during habituation and withdrawal. Figures 7 through 16 show that prior to introduction of the drug, all animals gained steadily in weight, and that three of the control rats continued to do so throughout the experiment. The experimental animals stopped gaining weight when the drug administration was begun. Rats #2 and #5 showed a weight loss from which they did not recover. When the drug was withdrawn, an increased rate of weight loss was noted in the experimental rats. After a few days, they began to gain weight, but at the end of the experiment, only two had reached their pre-drug weight.
Fig. 7. Weight during experiment.
Rat 1 (experimental).

Fig. 8. Weight during experiment.
Rat 2 (experimental).
Fig. 9. Weight during experiment.
Rat 5 (experimental).

Fig. 10. Weight during experiment.
Rat 6 (experimental).
Fig. 11. Weight during experiment.
Rat 9 (experimental).

Fig. 12. Weight during experiment.
Rat 10 (experimental).
Fig. 13. Weight during experiment.
Rat 3 (control).

Fig. 14. Weight during experiment.
Rat 4 (control).
Fig. 15. Weight during experiment.
Rat 7 (control).

Fig. 16. Weight during experiment.
Rat 8 (control).
DISCUSSION

This study has obvious limitations, especially in the small number of animals used, so that any wider application of the conclusions cannot be justified. However, the results show that in this group of animals the administration of morphine markedly reduced pain-elicited aggression, while similar injections of sterile water produced no such effect. Withdrawal of the drug resulted in a sharp increase in aggression. The same effects were observed in all experimental animals regardless of the way the drug affected them physically. Although three of the drug-habituated animals died, apparently from the effects of the morphine, the changes in their fighting behavior corresponded to those of the healthy animals. There appeared to be no direct correlation between changes in body weight and aggression, except perhaps upon withdrawal of the drug, when an increased rate of loss of weight was noted together with an increase in aggression. However, at least two of the rats were losing weight rapidly during habituation when rate of fighting was at its lowest. It must be concluded that, while weight fluctuations may also have been caused by the drug, the obvious physical effects
of the morphine were not directly related to its effect on aggression.

Nor can the reduction in aggression during habituation be attributed to the analgesic or depressant action of morphine. Beach (1957) has noted that the analgesic action of morphine "is exerted primarily on the anxiety associated with anticipation of pain, rather than on sensory thresholds of pain as such." Observation of the rats' behavior indicated that they did experience the shock, since they frequently jumped and squealed when the shock was administered. In addition, the results show that the first injection of 9 mg./kg. morphine almost eliminated fighting, even though this is regarded as a very moderate analgesic dose and should not have interfered with the experience of pain as elicited by the shock.

Although no quantitative measure of motor activity was available, qualitative observations led to the conclusion that the injection of morphine did not produce any marked or consistent depressant effects. When drug administration was begun, an initial decrease in activity was noted. After that, activity increased again, and in the case of two of the experimental pairs, reached what appeared to be a higher than baseline level. This is in accordance with the findings of Martin et al. (1963) who conclude that the depressant effects of
morphine become manifest before and are supplanted by excitant effects, as tolerance develops, and that the effects of morphine in the tolerant rat are primarily excitatory. Collins (1965) found that doses of 7 mg./kg. and 17 mg./kg. had no significant effect on the activity level of rats, as measured on an activity wheel. In his studies on the effect of morphine on exploratory drive, Beach (1957b) found that morphine-habituated rats engaged in more exploratory activity than their controls. Weeks (1964) habituated rats to doses of morphine as high as 40 mg./kg./hr., and demonstrated that they were then able to administer their own injections by pressing a pedal at regular intervals. When the dosage per injection was reduced, the rats responded by pressing the pedal more frequently. They were also able to press the pedal rapidly, an increasing number of times to obtain an injection as the ratio of pedal pressing to injection was increased. After obtaining the injection, the rats would frequently appear to doze off, but, if prodded, they moved normally without any evidence of the depressive effects of morphine. These findings suggest that morphine does not cause motor impairment and that the reduction in aggression observed in this study cannot be attributed to such impairment. Perhaps future research in this area should
include some attempt to discover what other behavior of the rat is affected by injections of morphine which reduce aggression.

While the foregoing discussion indicates some central action of morphine that suppressed aggression in all experimental animals, there were individual differences in reaction to other effects of the drug. All animals showed some degree of physical dependence, as evidenced by the observed discomfort and the continued weight loss which characterizes discontinuation of the drug to dependent animals, (Martin et al., 1963). Tolerance to the drug was noted in all animals, as indicated by the diminishing effect of a constant dose on fighting. However, there were differences in ability to tolerate increasing doses of the drug. Of the six experimental animals, one died during habituation, two during withdrawal, and a fourth showed a weight loss which was not being fully recovered at the conclusion of the experiment. The remaining two recovered rapidly from withdrawal distress. Since all animals were similar in age, weight and apparently healthy at the beginning of habituation, it is difficult to explain this difference in tolerance to the drug, especially when administered in such relatively small doses. It is tempting to agree with Nichols (1964), who has
noted that there are also individual differences among rats in their susceptibility to developing opiate-sustained behavior, and has concluded that:

"the weight of probability at this point seems to me to lie most heavily on a genetically-determined physiological difference which either aids or hinders the development of opiate-directed behavior. If there is a physiological influencer of addiction liability in rats, there may be a similar physiological influencer of addiction liability in man."
REFERENCES


