The Effect of Morphine on Conditioned Suppression and Response Topography of the Hooded Rat

Douglas Charles Reberg

Western Michigan University

Follow this and additional works at: https://scholarworks.wmich.edu/masters_theses

Part of the Psychology Commons

Recommended Citation
https://scholarworks.wmich.edu/masters_theses/3293

This Masters Thesis-Open Access is brought to you for free and open access by the Graduate College at ScholarWorks at WMU. It has been accepted for inclusion in Master's Theses by an authorized administrator of ScholarWorks at WMU. For more information, please contact maira.bundza@wmich.edu.
THE EFFECT OF MORPHINE ON CONDITIONED SUPPRESSION
AND RESPONSE TOPOGRAPHY OF THE HOODED RAT

by

Douglas C. Reberg

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

Western Michigan University
Kalamazoo, Michigan
June, 1967
ACKNOWLEDGEMENTS

For their generous contributions of time, equipment, and guidance, special thanks are due to Dr. David Lyon and Dr. Paul Mountjoy. I also greatly appreciate the efforts of Dr. Chris Koronakos for his encouragement and critical reading of the manuscript.

Douglas C. Reberg
MASTER'S THESIS

REBERG, Douglas Charles
THE EFFECT OF MORPHINE ON CONDITIONED SUPPRESSION AND RESPONSE TOPOGRAPHY OF THE HOODED RAT.

Western Michigan University, M.A., 1967
Psychology, experimental

University Microfilms, Inc., Ann Arbor, Michigan
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>CHAPTER</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Subjects 7</td>
</tr>
<tr>
<td></td>
<td>Apparatus 7</td>
</tr>
<tr>
<td></td>
<td>Procedure 8</td>
</tr>
<tr>
<td>III</td>
<td>11</td>
</tr>
<tr>
<td>IV</td>
<td>26</td>
</tr>
<tr>
<td>V</td>
<td>29</td>
</tr>
</tbody>
</table>

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
INDEX OF FIGURES

Figure 1. Total suppression ratios for individual subjects plotted as a function of increasing morphine dosage. 14

Figure 2. Sample cumulative records of individual subjects following saline injection. 17

Figure 3. Sample cumulative records of individual subjects following 45 mg./kg. injection of morphine. 19

Figure 4. Photographs of individual subject's response topographies with no injection administered. 22

Figure 5. Photographs of individual subject's response topographies following morphine injection. 24
INTRODUCTION

Psychological and pharmacological investigators alike have studied the effect of morphine on behavior, perhaps because of the serious problem of human abuse of narcotics. Examination of the literature shows most of the research to be in two main areas; the maintenance of behavior using morphine as a reinforcer; or, as in the present study, modification of some pre-established pattern of behavior by the administration of morphine.

Those studies falling into the first group in which morphine is used as a reinforcer may best be described in terms of the operant conditioning model as investigations of opiate-directed behavior (Nichols, 1963). The subject is thus described as escaping or avoiding aversive withdrawal syndromes by emitting a specified response upon which the administration of morphine is contingent.

Properly, then, opiate-directed behavior is interpreted as an escape or avoidance response (Nichols, Headlee and Coppock, 1956). Specific responses investigated as opiate-directed behavior have been: (1) head-orienting responses, where injections of morphine were contingent on rats' holding their heads either to the left or to the right (Headlee, Coppock, and Nichols, 1955); (2) taste discrimination, where rats learned to discriminate between morphine and other solutions in a situation where both were freely available (Nichols, Headlee, and Coppock, 1956; Davis and Nichols, 1962; Nichols, 1963; Claghorn, Ordy, and Nagy, 1965); (3) maze running, where rats were reinforced by stimuli previously paired with morphine injections (Beach, 1957); (4) bar
pressing in which morphine is administered to the subject through intravenous cannula after the completion of a specific number of responses (Weeks, 1962; Davis and Nichols, 1963; Thompson and Schuster, 1963; Week and Collins, 1964; Seal and Thompson, 1965). These studies in which well defined responses are established with morphine as a reinforcer have generally been accepted as demonstrating laboratory correlates of human addiction.

The present study, however, is representative of the other general area of research, in which the effect of morphine is measured in terms of the degree to which it modifies some pre-established patterns of behavior. The measures of behavior employed have varied in specificity. Some of the earlier research, for example, consisted of injecting subjects with morphine and making observations of subsequent spontaneous activity and responses in relatively simple operant situations. Working with cats, Wikler and Masserman (1943) observed that a dose of three milligrams of morphine per kilogram of body weight (three mg./kg.) resulted in a brief period in which no spontaneous activity was present, followed by an interval in which subjects' behavior was characterized by restlessness and distractibility. The same authors (Wikler and Masserman, 1943) observed morphine injections to result in suppression of bar-pressing, as well as the temporary abatement of an "experimental neurosis" defined as the behavior resulting from the pairing of an established feeding response with an air puff and electric shock. Similar observation techniques were later employed by Wikler (1944) in his investigations of the loci and mechanisms of the effect of morphine on the cat's
nervous system.

Other efforts have been concerned with the effect of morphine on human subject's behavior. The results of these studies (Hill, Kornetsky, Flanary, and Wikler, 1952b; Hill, Belleville, and Wikler, 1955) showed that morphine slowed reaction times under control conditions, but that when morphine was introduced into a situation where a penalty of an electric shock was imposed for relatively slow reactions, faster reaction times resulted. The conclusion drawn by these investigators was that morphine reduces disruptive effects on performance resulting from anxiety associated with the anticipation of pain. A similar anxiety reduction explanation was employed to account for the fact that morphine injections resulted in fewer overestimations of intensities of painful stimuli when compared with a standard (Hill, Kornetsky, Flanary, and Wikler, 1952a).

However, as a result of the multitude of ethical issues surrounding the act of injecting humans with a potentially dangerous drug and subjecting them to painful stimuli, many of the human studies have employed former drug addicts with a long history of drug exposure. Consequently, there is some uncertainty about the level of sophistication and applicability of "anxiety reduction" and similar accounts of the effect of morphine, as well as the representativeness of the subjects employed in most of these experiments.

In lieu of a satisfactory solution to the human subject problem, it is desirable to conduct animal research investigating the influence of morphine on established behavior, which provides a quantitative measure of the effect of the drug. This seems particularly important
when the proposed "anxiety-reducing" function of morphine is compared with much earlier findings with other organisms that morphine injections actually seemed to result in an increase of "distractibility", "irritability", and more acute "startle reactions" (Wikler, 1944).

A technique especially useful for the experimental analysis of "anxiety" is conditioned suppression (Estes and Skinner, 1941). This technique provides a quantitative measure of at least one aspect of emotional behavior, the disruption of other ongoing behavior. When rats are used as subjects, the procedure for establishing conditioned suppression begins with training the animals to press a bar for food on a schedule of reinforcement designed to yield very stable response outputs. At a given point in an experimental session, a stimulus is presented for a period of time, and is terminated continuously with a brief shock. After a few trials, the conditioned suppression phenomena becomes apparent in the complete or nearly complete cessation of responses during the interval in which the pre-shock stimulus is presented. The subject often displays other behavior during the stimulus, such as freezing, crouching and defecation. The degree of suppression is conventionally indicated by dividing the number of responses made during the pre-shock stimulus interval by the number of responses made in an equal interval immediately preceding the stimulus. Thus complete suppression is indicated by a quotient or suppression ratio of zero, and a complete absence of suppression is indicated by a suppression ratio of unity.
A number of investigators (Hill, Belleville, and Wikler, 1954; Hill, Pescor, Belleville, and Wikler, 1957) found that injections of morphine in rats where conditioned suppression was nearly complete resulted in a partial restoration of responding during the pre-shock stimulus. As dosages increased from two mg./kg. to 11 mg./kg., the restoration of responses became more complete with the suppression ratio approaching unity.

Although these findings appear to provide some evidence for the contention that morphine has "anxiety-reducing properties", they are somewhat restricted by the lower range of dosages employed. Because of the fact that an initial exposure to more than 11 mg./kg. of morphine ordinarily completely disrupts all behavior or is fatal, it is necessary to either limit the range of dosages, or, as in the present study, to habituate the animal to morphine using a sustained schedule of injections. By beginning at lower dosages with subsequent gradual increases, an increasingly greater amount of morphine is required to bring about a change in behavior, and the subject is thus able to survive doses that initially would have been fatal.

It was also reported by Brady (personal communication) that after injections of morphine subjects were observed to undergo great changes in response topography in the conditioned suppression situation, frequently biting and chewing the bar rather than pressing it.

The purpose of the present study, then, is to further investigate the effect of repeated injections of morphine at higher dose
levels than previously used, as well as making observations of possible changes of response topography associated with such an injection schedule.
METHOD

Subjects:

Five hooded rats from the colony maintained by the Western Michigan University Department of Psychology were used as subjects. All subjects, approximately 90 days old when training began, were weighed on five consecutive days with the average weight for each rat defined as that subject's free-feeding weight. The rations for each subject were then reduced until its weight decreased to 80 per cent of the free-feeding body weight.

In addition to the 12.5 grams of food received as reinforcement in the course of each experimental session, each subject was given supplementary rations of Purina Lab Blocks in order to maintain body weights within 10 grams of the 80 per cent free-feeding weights. Water was made available at all times.

All subjects were housed with the rest of the colony under laboratory conditions. One subject expired early in the morphine injection schedule, and its data was discarded in the final results.

Apparatus:

A Grason-Stadler response chamber constructed of aluminum with a plexiglas ceiling and front door was mounted in a light-tight sound attenuated chamber. A fan provided ventilation for the chamber, which was kept closed for all but two sessions in which photographs of the subjects were taken with a standard Kodak
Instamatic camera and flash unit.

The bar in the response chamber was mounted approximately three inches above the floor, and was adjusted to operate at approximately five grams of pressure. Reinforcements were delivered into a food cup immediately below the bar by an automatic feeder. The floor of the chamber was constructed of steel rods mounted approximately 1/2 inch apart, through which two milliamp shocks with 2.5 second duration were delivered to the subjects' feet through a slyambling unit and 50,000 ohm resistor.

Mounted outside the response chamber was the pre-shock stimulus, a six-volt D. C. buzzer, padded with foam rubber to reduce the intensity of sound to the point where it had no disrupting effect on bar pressing behavior in early presentations not paired with shock. Illumination of the chamber was provided by a shielded ten-watt bulb mounted above the plexiglas ceiling.

The procedure was programmed by appropriate timers and relay circuitry. The data were recorded from electrical impulse counters and a Gerbrands cumulative recorder.

Procedure:

Establishing Behavior Baseline

The bar press was established in all subjects on a continuous schedule of reinforcement, with each press of the bar followed by a presentation of a food pellet. When all subjects were pressing the bar steadily, a modification of the schedule of reinforcement
was introduced in which the food pellets were delivered on responses made after varying intervals of time, averaging a reinforcement every three minutes. Each experimental session was terminated after a subject received 50 reinforcements or remained in the response chamber for one hour, whichever event occurred first.

**Conditioned Suppression Procedure**

When the behavior of the subjects on the variable interval three minute schedule was marked by a fairly constant rate of response with relatively few long pauses, the conditioned suppression procedure was initiated. At about the 25th reinforcement during the session, the buzzer was turned on for a period of three minutes, and terminated contiguously with a two-milliamp shock of .5 seconds duration. The buzzer-shock pairings were repeated until complete or nearly complete conditioned suppression was regularly observed in all subjects. Complete conditioned suppression was defined as a suppression ratio of less than .1, where the number of responses made during the pre-shock stimulus divided by the number of responses recorded in the three minutes immediately preceding the onset of the pre-shock stimulus determined the suppression ratio.

In the final stage of the procedure, all subjects were first injected subcutaneously with ten minums of saline solution (a minum = approximately one drop) for at least three presentations of the shock in order to evaluate the possible effect of the potentially painful hypodermic injections on conditioned suppression.
Morphine Injection Schedule

When the actual morphine injections were begun, all subjects were given a dose of nine mg./kg., in a solution prepared such that one minum of solution contained one milligram of morphine. Since these subjects weighed an average of 200 grams, or 1/5 kilogram, a dose of nine mg./kg. meant that a subject received slightly less than two minums of morphine solution.

In each instance, however, this initial exposure proved to completely immobilize the subject, and in one instance was lethal. Consequently, the dosage was reduced to five mg./kg. and increased in subsequent steps to nine mg./kg., 15 mg./kg., 24 mg./kg., 36 mg./kg., and 45 mg./kg. All injections were administered 24 hours apart, subcutaneously on the ventral surface just anterior to the hind legs, alternating on the left and right sides. There was little evidence of irritation as a result of this procedure. With minor variation, subjects were placed in the response chamber immediately after receiving the injection. Conditioned suppression data were collected at the five mg./kg., nine mg./kg., 15 mg./kg., 24 mg./kg., 36 mg./kg., and 45 mg./kg. dosages, based on at least four presentations of the pre-shock stimulus at each dosage.
RESULTS

The analysis of the data for each subject was conducted in terms of total suppression ratios. These ratios were computed by (1) tabulating the number of responses made by the subject during all pre-shock stimulus presentations included for a particular dosage; (2) tabulating the sum of responses made in the three-minute periods immediately preceding all stimulus presentations included in sum (1); (3) dividing sum (1) by sum (2), with the resulting quotient defined as the total suppression ratio for that subject at that dosage.

The total suppression ratios for each subject, plotted as a function of increasing dosages are presented in Figure 1. All subjects showed complete suppression when injected with saline (total suppression ratios of less than .10). Injections of 45 mg./kg. produced a substantial reduction in suppression behavior for all subjects, with three of the four subjects showing the greatest reduction in these sessions.

The apparent diminishing effect of 45 mg./kg. injections on the suppression of subject 103 can possibly be attributed to the fact that the total suppression ratio is based on marginal data collected when the subject was in a greatly weakened condition due to self-inflicted injuries (described in detail below). A similar effect may be shown in the lower total suppression ratio for the subject 104 at nine mg./kg. dosage, as a sudden drop in the subject's weight and noisy breathing characteristic of a mild respiratory...
disorder were noted at that time. The failure of dosages less than 45 mg./kg., however, to produce any effect on the suppression behavior of subject 105 was consistently observed under normal conditions, indicating that intra-subject variation may be observed independently of any physical disorder.
Figure 1. Total suppression ratios for individual subjects plotted as a function of increasing morphine dosage.
Figure 2 presents sample cumulative recordings from sessions which followed 10 minute saline injections. The individual records in the figure are identified by the laboratory identification numbers assigned to each of the four subjects. Adjacent to the sustained deflections of the pen marking the periods in which the pre-shock stimulus was presented are the suppression ratios for the individual presentation, computed as described previously.

Each record includes a typical example of conditioned suppression, marked by the straight tracings made during the pre-shock stimulus intervals with corresponding suppression ratios less than .10. Although the overall response rates of these records show some individual differences, it was typical for each subject to maintain a constant rate of response throughout each experimental session.

Specimen cumulative records from sessions in which 45 mg./kg. dosages of morphine were administered are included in Figure 3. There are distinct differences between these records and the saline data in Figure 2. Conditioned suppression is greatly reduced, as shown by the increase in recorded responses during the pre-shock stimulus with corresponding suppression ratios greater than .10; and in contrast with the stable response rates observed after saline injections, each subject's rate was observed to gradually decrease as the session progressed and the morphine had a correspondingly greater effect. This is particularly evident in the record shown for subject 104, where the session was terminated due to a total absence of responses. The increased effect of the morphine injections is also reflected in the suppression ratios recorded for
Figure 2. Sample cumulative records of individual subjects following saline injection. (The individual records are traced on a moving strip of paper by a pen which moves toward the top of the paper each time the animal makes a bar press. Brief downward deflections of the pen mark deliveries of food pellets. Sustained deflections of the pen mark the onset of the pre-aversive stimulus, terminating contiguously with a .5 second shock. Reinforcements during that interval are marked by brief upward deflections of the pen. Suppression ratios for each pre-aversive stimulus presentation are indicated immediately above the interval).
Figure 3. Sample cumulative records of individual subjects following 45 mg./kg. injection of morphine. (See Figure 2 for explanation of records).
subjects 103, 105, and 106. For all of these subjects, later pre-shock stimulus presentations produced substantially greater suppression ratios than did the presentations occurring earlier in the session.

Photographs of bar-pressing response topographies typical of sessions where no morphine was injected and sessions where morphine was injected are displayed in Figures 4 and 5, respectively. The topographies of rats 104, 105, and 106 were similarly altered in the course of the injections schedule. In Figure 5, these subjects are pictured biting and chewing the bar after receiving morphine injections, compared with the pressing of the bar with the forepaws pictured in the preinjection photographs of these subjects included in Figure 4. Although these three subjects learned in early training to cease bar-pressing at the sound of the operation of the feeder to receive the reinforcement, it was also characteristic of their behavior after morphine injections to accumulate up to four reinforcements before consuming the pellets.

Rat 103 displayed a response modification quite different from that observed in other subjects. Much of the behavior of subject 103 after morphine injection consisted of chewing on its forepaws and tail as shown in the photographs of this subject included in Figure 5. This chewing dominated an increasing amount of the subject's responding as each session progressed, and at the end of the study it had gnawed two digits from its right forepaw and several pieces from its tail. Although no treatment was administered, these wounds were nearly always healed over at the beginning.
Figure 4. Photographs of individual subject's response topographies with no injection administered.
Figure 5. Photographs of individual subject's response topographies following morphine injection.
of each experimental session indicating that this behavior occurred primarily in the response chamber after morphine injections. It should be noted that such self-mutilation in rats is very rare under normal circumstances, but that this observation has been confirmed by Mountjoy and Roberts (personal communication) as a relatively common phenomenon among rats following a sustained exposure to morphine.
DISCUSSION

The data demonstrate that morphine introduced into the conditioned suppression situation produces effects on both the measured magnitude of suppression behavior and on the observed response topography.

The findings of Hill, et al (1954, 1957) that morphine results in a reduction of conditioned suppression are thus confirmed. Further, since the apparently reduced influence of morphine injections of 45 mg./kg. on the total suppression ratio of subject 103 can likely be attributed to the greatly weakened condition of the subject, the data suggest that higher dosages of morphine result in greater decrements in suppression behavior than those observed for lower dosages. This extends the findings of Hill, et al (1957) obtained for a lower range of dosages. The results also show that morphine produces marked alterations in response topographies associated with conditioned suppression. This observed modification of topography raises some important considerations in evaluating the apparent rate reduction observed after exposure to morphine.

A normal bar-press is a highly stable response pattern, primarily because in the course of development a response of a minimum force is necessary to operate the bar and obtain a reinforcement. Weaker responses are therefore not reinforced, and ultimately are extinguished. The resulting response is practically always recorded, and the assumption is therefore justified that a reduction in recorded rate accurately reflects an actual reduction
in the bar-pressing behavior of the subject.

In the case of the bar biting responses produced in three of the subjects in the present study, however, many of the responses were not recorded; either because the subjects frequently held the bar down with a forepaw while making several biting responses, or made a number of biting responses before the bar was depressed far enough to record one response. Consequently, the reduced rates of response recorded for subjects 104, 105, and 106 do not necessarily represent a reduction in bar-biting activity.

It is also important to note that because of the nature of the topography alteration produced by morphine in subject 103, a recorded response rate decrease for that subject did reflect a corresponding decrease in bar-pressing activity. However, this decrease was associated with a marked increase in other behavior, specifically paw and tail-chewing.

The implication of these observations is that the effect of an extended series of morphine injections should not strictly be viewed as a decrease in activity. An interpretation more in line with the present observations is that morphine injections administered in a series produce a modification in behavior such that the apparent decrease in response rate may be attributed to the alteration of response topography. In the case of the bar-biting response produced in subjects 104, 105, and 106, many responses were unrecorded because the apparatus was not designed to effectively record the modified topography. In the case of the paw and
tail-chewing behavior produced in subject 103, the resulting response was incompatible with bar-pressing. Whichever modification occurs, a description in terms of rate reduction as an outcome of an extended schedule of morphine injections which implies a corresponding reduction in general activity is an inaccurate account.

The absence of any effect on the total suppression ratio of subject 105 by morphine injections of less than 45 mg./kg. was associated with topography modifications identical to those observed for subjects 104 and 106. In view of the fact that this topography change appeared independently from the influence on suppression behavior, it is clear that the two effects of morphine observed here may not be closely related, and that the topography alterations introduced by morphine injections may not be unique to the conditioned suppression situation. At the very least it indicates that there are a number of experimental parameters involved in the effect of morphine which influence behavior in a more complex manner than can be adequately accounted for in terms of "anxiety."
REFERENCES


Brady, J. V. (personal communication).


Seal, D. & Thompson, T. Telemetry-controlled system for chronic drug self-administration in unrestrained monkeys. Report # PR 65-5, Department of Psychiatry, University of Minnesota, Minneapolis, 1965.


