EFFECTS OF MORPHINE ON LEARNED ADAPTIVE RESPONSES AND EXPERIMENTAL NEUROSES IN CATS

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The effects of opiates on the behavior of experimental animals have been described by several authors, the more detailed accounts being those of Tatum, Seevers and Collins (rabbit, cat, dog and monkey), Kolb and DuMez (monkey) and Spragg (chimpanzee). These investigators were primarily concerned with the development of tolerance to and the signs of physical dependence on withdrawal of the drug. The descriptions relating to behavior are therefore confined to the spontaneous activity of the animals, although Spragg included an account of the performance of the chimpanzee on tests of delayed response and multiple choice during addiction to and withdrawal of the drug. The present report is concerned with the effects of morphine on spontaneous behavior, "conditioned" responses and experimentally produced "neuroses" in cats.

METHODS

Five healthy cats were used in these experiments. With 1 exception none of these cats had ever before been used for experimental purposes. The animals were permitted to have plenty of water but were fed only in the observation cage during each of three to five day periods of experimentation.

The first series of experiments consisted of control observations on the effects of the intraperitoneal injection of morphine sulfate in doses of 0.5 to 6 mg. per kilogram of body weight on the spontaneous behavior, feeding habits and responses of each cat.

In the second series of experiments, each cat was placed in the "automatic conditioning apparatus" described by one of us (J. H. M.) and trained successively to eat from the food box in the cage, to lift the lid of the food box with its nose and then to respond to a light-bell signal by running to the food box to eat a pellet dropped by the automatic feeder. The animal was then further trained to initiate its own feeding responses by operating a platform switch which actuated the conditioning signals. Finally, the switch was placed behind a movable transparent barrier which the cat could pass if it squeezed itself through the space between the edges of the barrier and the walls of the cage. Three of the cats (1, 2 and 5) learned to do this with ease and continued to operate the switch and to respond to the feeding signals as before. The other 2 cats were not taught the technic of switch manipulation but continued to respond to signals given by the operator. With all animals, responses to signals were rewarded by use of the automatic feeder, which dropped a pellet of food in the food box only after the correct responses had been made by the animal. After these behavior patterns were firmly established, each animal was given an intraperitoneal injection of morphine

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sulfate, and its reactions to the same stimuli in the experimental situation were observed over a period of six to nine hours and then again on the following day.

In the third series of experiments, the feeding responses previously described were disrupted by subjecting the animal to a combined stimulus of air blast and grid shock just as it lifted the lid of the food box in response to the light-bell signal. The air blast consisted of a harmless puff of air directed to the side of the animal's face and was accompanied by a rather loud, sudden noise. The grid shock was administered by connecting the grid floor of the cage to a condenser fence electrifier. The "neurotic" alterations in behavior induced in the animal by this technic were then observed over a control period of two or three days, and the procedure was repeated once daily. When these behavior patterns were definitely established, the animal was given intraperitoneal injections of morphine sulfate in order to determine the effects of this drug on the cat's spontaneous behavior and on its responses to conditioned stimuli and other experimental procedures.

RESULTS

Effects of Single Doses of Morphine Sulfate on Spontaneous Behavior.—Vomiting or defecation or both appeared regularly within five minutes after the injection of 3 mg. of morphine sulfate per kilogram of body weight. In 4 of the 5 cats studied this was followed by a period of "sedation," lasting one-half to two hours, during which the cat sat quietly in the corner, paying no attention to stimuli, such as sudden noises, flashes of light or the entrance of strangers into the room. The pupils were regularly dilated. The cat also ignored food placed before it and offered less resistance to handling than it did before the injection of morphine. This initial period of inactivity, however, was gradually replaced by one characterized by restlessness and distractibility. The cat sat quietly in its cage, but on the approach of the experimenter it would walk about, rub its face and neck against the side of the cage and resist handling more than before the injection of morphine. However, this behavior was not accompanied by any evidence of "rage," although a brief "startle reaction" was frequently elicited by a sudden stimulus. When food was placed before the animal, it ate readily but was distracted by other stimuli and thus continued to change from one activity to another. Slight ataxia appeared during this period, persisted for about four hours and then gradually subsided. By the following morning the cat was apparently entirely normal and behaved as before the injection of morphine.

One animal (cat 4), however, exhibited no initial period of inactivity, increased distractibility occurring within a half-hour after injection. Repetition of the dose at this time accentuated the restlessness and distractibility. At times behavior suggestive of hallucinosis appeared in that the cat made sudden dashes toward corners or under radiators or doors, and at other times it seemed to be playing with a nonexistent mouse. On the following morning this cat's behavior was entirely normal, and it appeared to have recovered completely from the effects of the drug.

Doses of approximately 1 mg. per kilogram produced the same sequence of events in each animal, except that vomiting and/or defecation appeared only rarely. This amount was therefore adopted as the basic dose for subsequent experiments.

Effect of Single Doses of Morphine Sulfate on Conditioned Responses.—In general, in the 4 cats which exhibited early "sedative" effects, progressive dissolution of the response patterns took place in the order of decreasing complexity. Thus, about two or three minutes after the intraperitoneal injection of morphine, the cats ceased to pay attention to the platform switch, although they still responded well to the light-bell signal when the latter was manipulated by the experimenter. A few minutes later they failed to respond to this signal but would still eat from the box when shown the food. Shortly afterward (five to ten minutes after injection) the cats ignored food as well, and also refused to eat outside the observation cage. This behavior continued unchanged for from one-half to two
hours, after which they would again eat from the food box, but still ignored both switch and light-bell signals; the only response to the latter was a curious, investigatory gaze in the direction of the light or sound, without any sign of recognition of the stimulus as a signal for food. Three or four hours after injection the cats responded to the light-bell signal with varying degrees of consistency but still ignored the switch. One animal (cat 1) finally also operated the platform switch while still restless and highly distractible. When they were retested the next morning, after the effects of the injection had worn off, all 4 cats operated the switch and responded to signals as well as before injection.

The sequence of events with cat 4, which exhibited no "sedative" period after injection, was the same except that the rate of disappearance of the conditioned responses was much slower and recovery was more rapid than with the other animals. On the other hand, this cat failed to operate the switch the next day, and it had to be retrained to do so.

Effects of Single Doses of Morphine Sulfate on Experimental Neuroses.—In general, the types of behavioral aberrations produced in these experiments conformed to those already described by one of us (J. H. M.). The "neurotic" animals ignored the platform switch and would not eat from the food box, even when the lid was raised and salmon-covered pellets of food were displayed in full view. Attempts to force the cat's head into the food box were vigorously resisted by the starving animal, and if the door of the cage was left open, the cat invariably attempted to escape. Cat 2 persistently closed the platform switch but paid no attention to the signals thereby produced. In response to the light-bell signal, cat 3 vocalized and rolled about on the grid floor of the cage. Cat 5, which had been subjected to motivational conflicts before injection and which had then been relieved of its "neurosis" by experimental means, again exhibited marked terror in response to the light-bell signal and tore wildly at the doors of the cage or scurried behind the glass screen. These reactions were all accentuated on exhibition of the stimuli which had previously acted as conditioned signals for feeding. These behavioral changes, once established, persisted unchanged in spite of continuous starvation over a period of four days. An interesting observation, however, was that on the first trial each morning the responses were frequently near normal, but the characteristic neurotic reactions developed on the second or third trial, immediately afterward, without reinforcement by air blast or grid shock.

After the intraperitoneal injection of 1 mg. of morphine sulfate per kilogram of body weight, cats 1, 2, 3 and 4 continued to exhibit the aberrant behavior previously described and refused to eat for four or five hours. Then, despite the persistence of some manifestations of anxiety at the stimuli, feeding responses reappeared, first outside and then inside the experimental cage. About one hour later the "neurotic" behavior of cats 1, 3 and 4 disappeared completely, although some degree of restlessness and distractibility remained. Shortly afterward, cat 1 responded regularly to the light-bell signals, and cats 3 and 4 did likewise, although less consistently. Finally, about seven hours after the injection of morphine, cat 1 exhibited no evidence of "experimental neurosis," occasionally operated the platform switch and sometimes responded to the light-bell signal thereby evoked in a normal manner. When they were retested the next morning, however, after the effects of the morphine had worn off, the behavior of cats 1 and 3 was fully as "neurotic" as on the previous morning, before the injection of the drug. In contrast, cat 4 appeared to have been "cured" completely of its "neurosis" although the platform

switch response was completely extinguished, and the responses to the light-bell signals were more erratic.

The initial dose of morphine administered to cat 2 appeared to have little effect on its aberrant behavior. The animal continued to behave as before, although with increased distractibility. The next day twice the dose of morphine sulfate (2 mg. per kilogram) was given intraperitoneally. Considerable diminution in the intensity of the "neurotic" signs was noted about three hours after injection, and there was no evidence of "neurosis" two hours later. About this time feeding responses in the cage reappeared, and these were followed shortly by fairly consistent and correct responses to the light-bell signal. The behavior of this cat was observed until about seven hours after injection, but no further manipulations of the switch were noted. On being retested the next morning, the behavior of this cat, too, was fully as abnormal as before the administration of morphine.

The reaction of cat 5 to morphine was quite different. As already noted, this cat had previously been made "neurotic" by the same technic as that employed in the morphine experiments but had been "cured" by various therapeutic technics (Masserman*) before being used in these experiments. After the neurosis had been reprecipitated in severe form by a repetition of the blast-shock experience, morphine sulfate, even in doses of 2 mg. per kilogram, had no effect on the terrified, panicky reactions to the light-bell signals. The dose was repeated at two hour intervals, but the animal's fearful responses continued unabated, even though restlessness and distractibility were present. A few minutes after a total dose of 7 mg. per kilogram had been given, the respirations suddenly became slowed, and, after a few gasps, the animal died, apparently of respiratory paralysis. Just before death, extreme extensor rigidity of all four legs was noted, and this persisted after death, so that the dead animal could be placed in a standing position.

SUMMARY AND CONCLUSIONS

1. In 4 out of 5 cats, morphine in doses of approximately 1 mg. per kilogram of body weight regularly produced refractoriness to stimuli and diminution in activity, lasting from one-half to two hours, after which the animal became more restless and evinced notable distractibility over a period of about six to seven hours. The fifth cat exhibited only the latter type of behavior with this dose of morphine.

2. In all animals learned adaptive responses were greatly affected. The more recently acquired and most complex learned responses disappeared first, and then reappeared last, as the effects of the drug wore off. The disintegration of learned complex responses was usually complete within ten minutes after injection, while reversal of this process began three or four hours later in most cases.

3. "Experimental neuroses" were produced by creating an impasse between conflicting motivations of hunger and fear. The complex "neurotic" behavior abated with injection of morphine and was replaced by previous adaptive patterns about five or six hours after the administration of the drug. However, in 3 of the animals the "neurotic" behavior reappeared in full force after the effects of morphine had worn off further, although a cat which had been made only mildly "neurotic" showed notable diminution in its abnormal reactions the next day. In contrast, an animal with a reprecipitated and severe neurosis showed no improvement with doses sufficiently large to cause its death.

*Masserman, J. H., and Wikler, A.: Effects of Morphine on Adaptive Patterns and Experimental Neuroses in Cats, motion picture film, distributed by the University of Chicago.