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Behavioural Effects of a Prolonged Treatment with Small Doses of Morphine in Cats

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The present experiment was designed to answer the following questions: Using an operant conditioning situation, will it be possible to detect behavioral effects of doses of morphine corresponding to human clinical doses? How will these effects, if any, develop with repeated administration? Is operant behaviour a sensitive measure of withdrawal reactions?

Methods

Subjects. Subjects were three cats, weighing about 2.5 kg, numbered 10 (male), 11 (male) and 12 (female). They were from the same litter, born in the laboratory and approximately 18 months old when the experiment was started. They lived in the animal room in large home cages ($180 \times 60 \times 55$ cm). Cats 10 and 11 were housed together; 12 was alone. They had not been used as subjects in pharmacological experiments before, but had worked in the operant conditioning situation since the age of 10 months. They were fed with the milk obtained as reinforcement during the experimental sessions (or an equivalent amount, 75 ml, given in the home cage when no experiment was run), plus 50 g of boiled meat per day.

Apparatus. A home-made Skinner-box was used, equipped with a response lever (telegraph-key) and a tray. Milk was delivered into the tray through a solenoid valve. The experimental operations were automatically controlled. The experimental events were recorded on a Gerbrands cumulative recorder and on a series of digital counters. The experimental cage was isolated, in a separate rooom, from the auditory signals of the control units.

Schedule of reinforcement. The schedule of reinforcement was a fixed Interval 2 min (FI 2). The distribution of responses in the interval was

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obtained by recording, on 8 digital counters, the responses emitted during the eight successive 15 sec periods subdividing the 2 min interval.

Drug administration. Morphine hydrochloride was injected subcutaneously at a dose of 0.2 mg/kg, 15 min before the experimental session. This dose is equivalent, relative to body-weight, to an average therapeutic dose used with humans in clinical practice.

Dextromoramide (Palfium)[1] was used with cat 10 at the same dose, in the same conditions.

Experimental program. Experimental sessions lasted 1 hr and took place daily, with a few exceptions. During the pharmacological treatment, the drug was injected irrespective of whether the animal was run in the experimental cage on that day or not.

Cats 11 and 12 underwent the same treatment.

After 32 sessions of training, a fairly constant baseline behaviour was obtained and the morphine treatment was started. The drug was injected daily without interruption during 43 days, the number of experimental sessions amounting to 35. Then the drug was withdrawn for 5 days, during which the animals were run in the experimental cage. Another series of morphine injections was started, which lasted for 48 days, with a total amount of 36 experimental sessions, followed by 17 sessions without drug. The animals were rested for 2 weeks and then again put to work, without drug, for another experiment using the FI Schedule.

The experimental program was different for cat 10. After the first series of morphine injections and 3 days of drug withdrawal, during which a very pronounced withdrawal reaction was observed, the morphine—and subsequently Palfium—treatment was reinstated and interrupted alternately for short periods, according to the following schedule:

Treatment	Number of days	Number of sessions
1. morphine	15	10
2. no drug	3	3
3. morphine	9	7
4. no drug	23	17
5. Palfium	9	9
6. no drug	9	7

As the behaviour remained markedly deteriorated throughout series 3 and 4, with and without morphine, an attempt was made to substitute Palfium for morphine, in the hope that this drug, sharing several therapeutic properties with morphine, and being also liable to induce addiction, would eventually help in reinstating operant behaviour.

[1] Kindly supplied by Janssen Pharmaceutica.

Results

Two aspects of the behaviour controlled by an FI schedule of reinforcement can be used as measures of pharmacological action: 1. the overall rate of responding, or the total output per experimental session; 2. the distribution of responses through time. Pre-drug control values for both aspects were obtained by averaging results from the last ten sessions before treatment for each individual subject. Pre-drug average total output is shown as reference line across the graphs in Fig. 1 (solid lines), together with the limits of one standard deviation above and below the mean (broken lines). Samples of normal pre-drug behaviour are given, for cats 10 and 12, in Fig. 2 and 3, curves A. These curves show the typical pattern of behaviour generated by the FI schedule: the animal pauses after each reinforcement and resumes responding at an increasing rate toward the end of the interval. The pre-drug time discrimination is shown, in histogram form, for each cat, in Fig. 4, column A. The height of each block in the histogram corresponds to the percentage of responses emitted in each of the eight 15 sec periods subdividing the interval.

1. Effects of morphine on conditioned behaviour

In all three subjects, morphine produced an increase of conditioned activity. This effect, however, was not observed immediately in the first days of chronic treatment. It appeared only after several daily injections (5—12). It subsided, to show up again in later phases of the treatment. The graphs in Fig. 1 show the fluctuations of the total output throughout the treatment: periods of increased activity alternate with periods of normal and of depressed activity. Peaks of activity as high as six standard deviations above pre-drug means are observed in cats 10 and 11. The total output reached 775 responses at the tenth session under morphine in cat 10; the average pre-drug level was 326 with a standard deviation of 68. In Cat 11, the total output oscillated between 868 and 983 in five consecutive sessions (10th to 14th of the morphine treatment); the average pre-drug level for this animal was 332, with a standard deviation of 103. Cat 12 showed in the pre-drug phase a greater session-to-session variability than cats 10 and 11; its average total output was 563 with a standard deviation of 187; the peak of activity in the first phase of the treatment was reached on the 12th session under morphine with 959 responses.

Similarly to the total output, the distribution of responses in time remained unaltered during the first few days of the treatment. It was modified in all three cats during the first phase of increased activity. This effect was transitory and, except for a few later sessions in cat 12, it did not appear during the subsequent periods of increased activity.

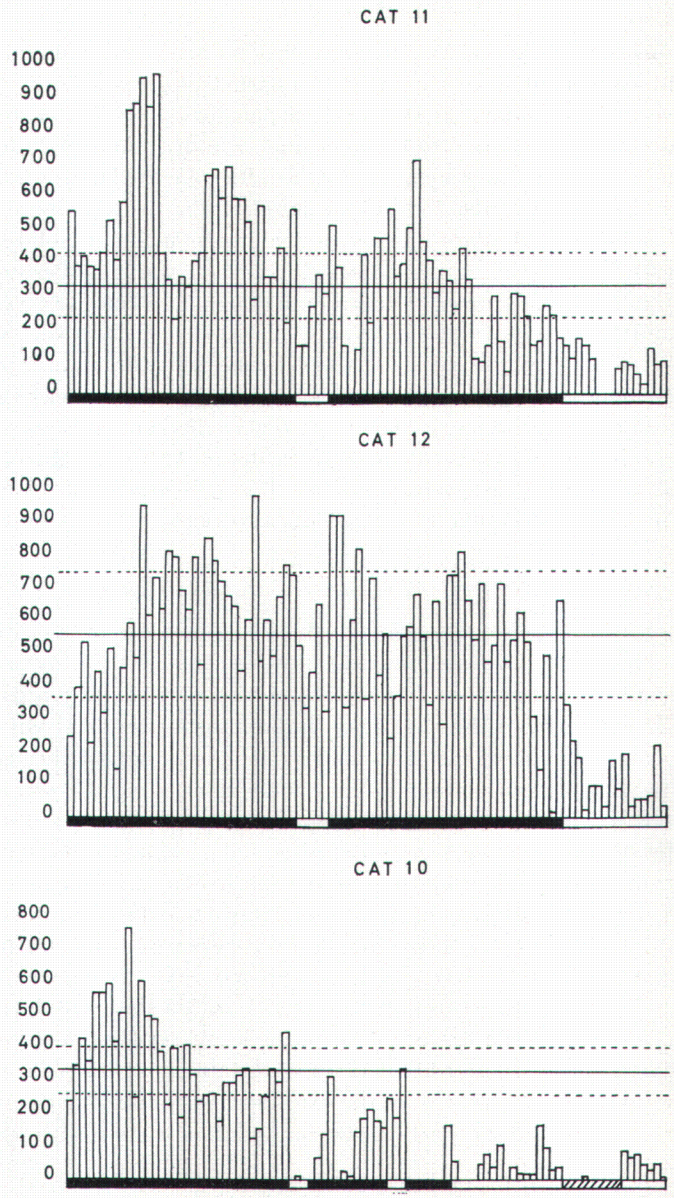

Fig. 1. Rate of responding during morphine treatment. Ordinate: number of responses. Abscissa: successive experimental sessions (one block of the histogram corresponds to one session). The solid line across the graphs corresponds to the pre-drug control mean, used as reference point to assess the effect of drugs; the dotted lines correspond to one standard deviation above and below this pre-drug mean. A black bar underlining the blocks indicates sessions under morphine; a hatched bar: sessions under Palfium; a white bar: sessions without drug

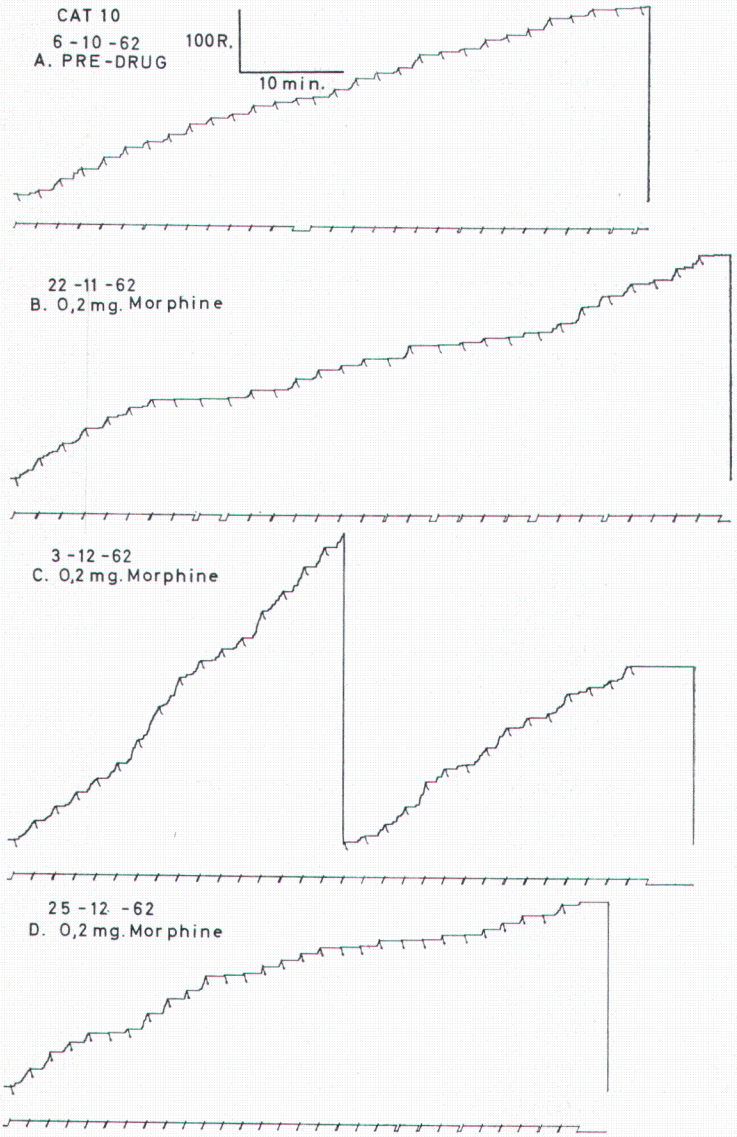

Fig. 2. Samples of cumulative curves from Cat 10, (*A*) prior to treatment, (*B*) in the very first stage of treatment, (*C*) in the phase of behavioural effects of morphine and (*D*) after tolerance had developed. Responses are cumulated on the ordinate; the abscissa corresponds to time; reinforcements are indicated by oblique pips cutting the cumulative curve; the pen tracing the horizontal line at the bottom of each graph is deflected when the 2 min delay has elapsed and comes back to its original position as soon as a reinforced response is emitted

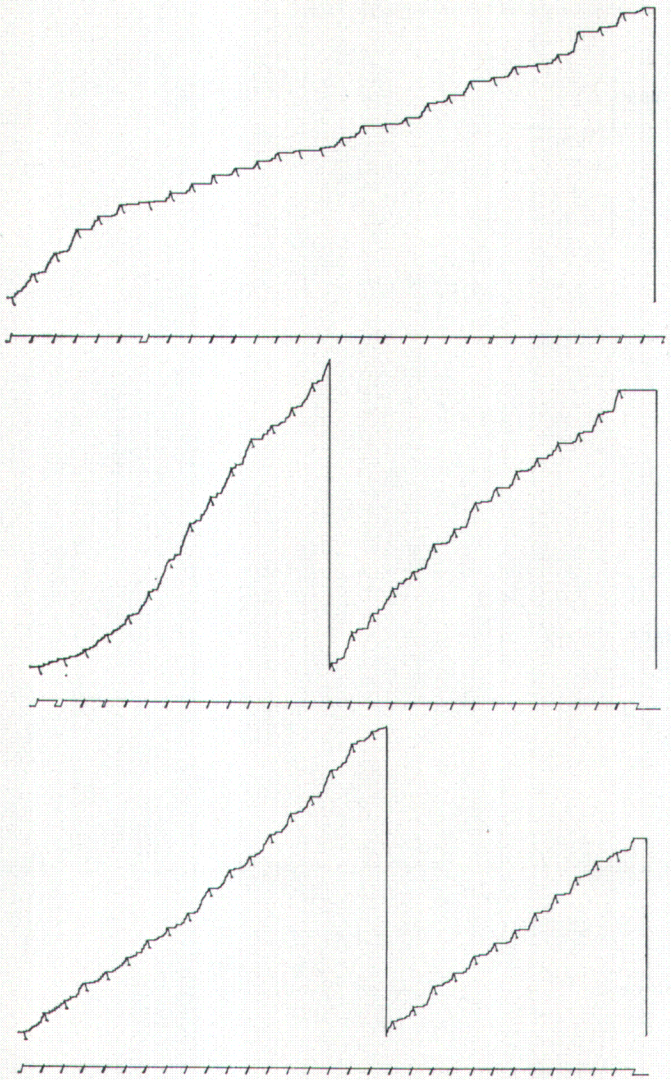

Fig. 3 (first half).
Samples of cumulative curves from Cat 12, (*A*) prior to treatment, (*B* and *C*) during the phase of behavioural effects of morphine, (*D*) after tolerance had developed, (*E*) after the drug was withdrawn for the first time, (*F*) after new treatment when the drug was withdrawn for the second time

The curves from cat 10, reproduced in Fig. 2, show the absence of effect at the beginning of the treatment (curve B, first session with drug), the disruption of the regular pattern a few days later (curve C) and the normal behaviour reinstated after 1 month of treatment (curve D). Curves B and C in Fig. 3 show the effects of morphine on Cat 12; curve D

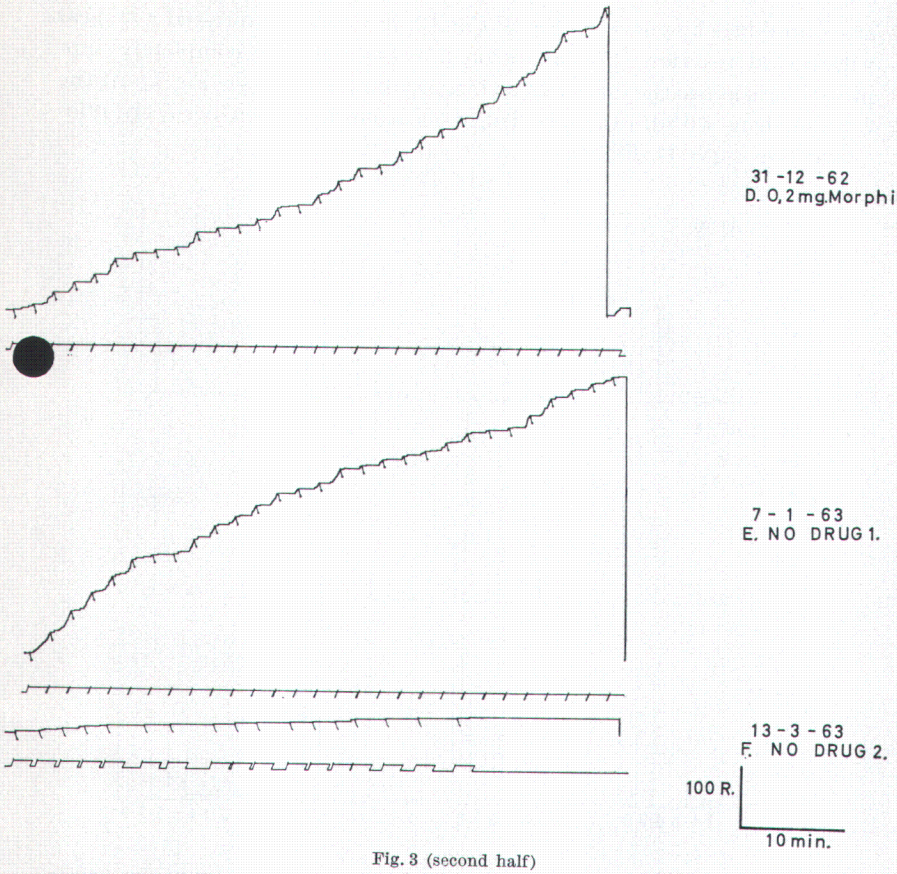

Fig. 3 (second half)

was obtained after 5 weeks of treatment when the behaviour had come back to its pre-drug pattern.

Typical alterations of temporal patterns are shown in histogram form in Fig. 4. Morphine histograms are from individual sessions selected (B) from the very first phase of the treatment, while the drug showed no effect, (C) from the deterioration phase and (D) from the later phase, in which the normal temporal pattern was restored. The percentage of responses emitted during the last 15 sec of the interval drops from a normal level of 53, 48 and 41 to 31, 31 and 28 for cat 10, 11 and 12 respectively, in the phase of deterioration under morphine (column C).

2. Effect of withdrawing the drug on conditioned behaviour

Administration of morphine was interrupted for the first time after 6 weeks of treatment. This interruption did not produce any effect on conditioned behaviour in cats 11 and 12. Normal curves were obtained,

as examplified by curve E, Fig. 3. Cat 10, however, manifested a typical withdrawal reaction: the conditioned behaviour was completely suppressed as soon as the drug was no longer administered (see Fig. 1). At the time of drug withdrawal, pre-drug behaviour had been perfectly reinstated (see curve D, Fig. 2).

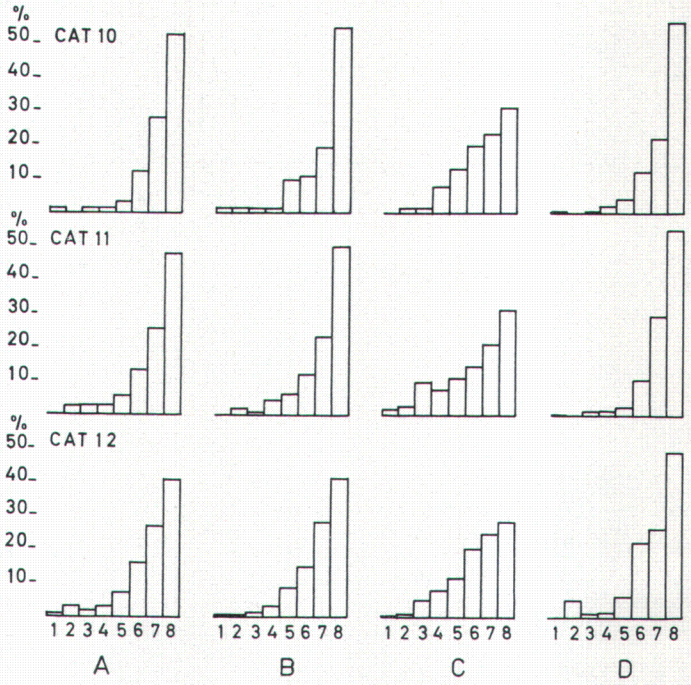

Fig. 4. Histograms showing the quality of temporal discrimination for each cat (*A*) in pre-drug sessions, (*B*) in the first phase of morphine treatment, (*C*) in the deterioration phase, and (*D*) in the later phase after behavioural tolerance has developed. Each block of the histograms, numbered 1—8, corresponds to a 15 sec period subdividing the 2 min interval. The height of each block is proportional to the percentage of responses emitted during the corresponding 15 sec period

After 5 days without drug, cats 11 and 12 were submitted again to chronic treatment for 7 weeks. When morphine administration was interrupted for the second time, after this period, both animals showed, within 3 or 4 days, a marked deterioration, followed by complete suppression of conditioned behaviour. A typical curve, on the way to total suppression, is shown in Fig. 3, F. The experiment was continued for 3 weeks without drug. This was not enough for the animals to resume normal responding in FI, as indicated by the right end part of the graph in Fig. 1.

In Cat 10, it took 2 weeks of morphine administration to reinstate a pattern of behaviour close to normal baseline (though the overall rate remained depressed). A new interruption did not produce immediate

effects; possibly, 3 days were not enough to show an effect, as was found later on in the experiment when the drug was withdrawn with cats 11 and 12 (see Fig. 1). From then on, the behaviour of Cat 10 became very erratic. The conditioned activity was generally completely or almost completely absent, during a further week with drug and 3 more weeks without drug. An attempt was then made to substitute Palfium for morphine. This drug produced a complete suppression throughout the 10 days during which it was administered. When Palfium injections were interrupted, the animal resumed responding in the experimental sessions for the first 15 min or so, and would then stop until the end of the hour.

After a rest period of 2 weeks, the subjects were run again on the same schedule of reinforcement, starting another experiment. Normal FI behavior reappeared in all three animals within 3—4 sessions. This indicates that the behavioural modifications induced by morphine were not irreversible.

Discussion

The present study was purely behavioural in scope. However, some of the results are puzzling, when compared with what might have been expected on the basis of pharmacological data concerning morphine action.

First, behavioural changes appeared under clinical doses of morphine, provided that the drug was administered repeatedly during a few days. The effect is probably due to some cumulative process, though such a hypothesis was never required in other studies of morphine action. It might be that the behavioural technique used in our experiment is sensitive enough to reveal effects at doses which do not induce the type of phenomena usually looked for by pharmacologists. It should also be noted that, in two cats, the withdrawal reactions did not show up immediately, but only after 3 or 4 days: this fact provides another argument for a possible cumulative process.

Secondly, tolerance to the behavioural effects of morphine, e.g. increased conditioned activity and modifications of timing behaviour, was observed. This finding is surprising since experimental conditions were least favorable to the development of tolerance. As a rule, the morphine type of tolerance develops only under adequate conditions of dosage and frequency: small doses, administered at long intervals, do not usually induce tolerance (Seevers and Deneau, 1963). Tolerance to the excitant effects of morphine is reported to occur in cats with doses of 2 mg/kg, in fact ten times larger than ours (Eddy and Himmelsbach, 1936).

Behavioural tolerance itself may be considered, in some cases, hypothetically, as the result not of pharmacological tolerance to the drug, but of some corrective mechanisms at the behavioural level (Dews, 1962). This kind of hypothesis should not be retained without direct and specific

experimental evidence (RICHELLE, 1965). Furthermore, in the present case, it would not account for the clearcut behavioural reaction to the interruption of morphine treatment.

Thirdly, the immediate or progressive suppression of conditioned behaviour when the drug was withdrawn seems to imply physical dependence. The cat is considered as a poor test subject to show physical dependence to morphine (SEEVERS and DENEAU, 1963). Here again, behavioural techniques might reveal themselves better suited to show subtle effects. However, the same question arises here as for tolerance: how did physical dependence develop with such small doses, administered at 24 hr intervals, when it is generally admitted that this requires continuous exposure of nervous cells to the action of the drug? Physical dependence may be obtained with relatively small doses, provided that they are administered at short intervals. Thus, it occurs in the monkey with doses as small as 100 μg/kg administered every 6 hrs (SEEVERS and DENEAU, 1963).

The problems raised by this experiment naturally lead to further research, in which behavioural analysis of morphine action should be systematically related to the results of careful investigations by means of classical pharmacological methods.

Summary

Three cats, conditioned to respond for food in a Skinner-box on an FI schedule of reinforcement, were submitted during 3 months to chronic treatment with daily doses of 0.2 mg/kg morphine hydrochloride. After an initial phase where no effect was observed, the subjects manifested increased responding and a deterioration of timing behaviour. Behavioural tolerance was shown to develop to both effects. Withdrawing the drug resulted in the immediate or progressive suppression of conditioned activity. The findings are discussed by reference to generally accepted conceptions of tolerance and physical dependence.

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