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Chronic morphine consumption decreases wheel running and wheel running-reinforced behavior in rats

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Abstract

The purpose of this experiment was to evaluate the effects of morphine self-administration on wheel running and wheel running-reinforced lever pressing in rats. The home cage was equipped with a bottle that contained either water, a saccharin-flavored 0.5-mg/ml morphine solution, or saccharin (0.25%). The bottle was available for either 1 or 3 h. The bottle was then removed, and 20–22 h after removal, the rats were moved to an operant chamber in which lever presses earned 15 s access to a running wheel (according to a variable interval (VI) 40-s schedule). The morphine condition was in effect for 69 days, and consumption gradually increased to a level of 67 mg/kg/day. During the morphine condition, wheel running and lever pressing decreased. Following the removal of morphine, (so that the home-cage bottles provided a 0.25% saccharin solution), the two instrumental behaviors increased to the pre-morphine (water) levels. However, the increases were not immediate, and in the first post-morphine session, lever pressing and wheel turning remained at the depressed morphine level. The post-morphine increase in lever pressing was substantially larger than the increase in wheel running. The results support the hypothesis that chronic opiate consumption reduces the frequency of some nondrug-related behaviors, and that this, in turn, increases preference for the opiate.

Keywords: Morphine self-administration; Wheel running; Opiates; Drug addiction; Choice; Rats

1. Introduction

According to the American Psychiatric Association's description of drug dependence (American Psychiatric Association, 1994), the progression from casual to heavy drug use is often accompanied by a decrease in conventional activities, such as family life and professional commitments, and an increase in drug-related activities. This progression suggests that a common property of addictive drugs is the capacity to reduce the rewarding value of competing activities (Heyman, 1996). The interactions may be indirect or direct. For example, the social consequences of illicit activities, such as secrecy, are likely to interfere with the pursuit of conventional responsibilities at work and home. Or drug-induced changes in the biological substrates that mediate reward could differentially reduce the value of conventional reinforcers. In support of a direct mechanism is an experiment by Wise and Munn (1995). In a self-stimulation procedure, they found that chronic amphetamine treatments increased the level of brain stimulation necessary for maintaining responding. That is, reward efficacy declined, and the effect persisted after the termination of amphetamine treatment.

The experiment presented in this report tests the generality of Wise and Munn's findings. The rats were exposed to morphine rather than a stimulant, and the reinforcer was wheel running. Unlike food and water, wheel running is a nonconsummatory reward, and unlike brain stimulation, it can be considered a "natural" reward. However, as with food, water, and brain stimulation, it maintains lever pressing, and quantitative relationships between lever pressing and contingent wheel running approximate those found with consummatory reinforcers (Collier and Hirsch, 1971; Belke and Heyman, 1994). The experiment also differed from previous studies in that the rats consumed the drug for several months rather than several weeks. Thus, the study tests whether an extended period of morphine consumption

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influences wheel running and the capacity of wheel running to function as a reinforcer for lever pressing.

2. Method

2.1. Subjects

Eight male Wistar rats served as subjects. They were selected from a group of 16 on the basis of higher initial wheel-running rates. They were approximately 60 days and weighed on average 251 g just prior to the start of the experiment. During the course of the experiment, food intake was restricted so that their body weights were initially lowered to about 85% of ad lib weight. After each session, the rats were fed 12–14 g of chow. On this diet, they gained approximately 5 g a month, reaching a weight of about 113% of ad lib weight at the end of the experiment (283 g).

2.2. Apparatus

The apparatus consisted of two standard activity wheels mounted in soundproof chambers. Each wheel was 35.5 cm in diameter, and had Plexiglas walls on the sides. A 7×9 cm opening located in the center at the base of the right wall allowed the animal to be placed in the apparatus. A retractable lever mounted at the opening of each wheel could be extended 1.8 cm into the interior of the wheel. A solenoid-operated rubber brake could stop the wheels. A 24-V dc light located near the brake illuminated the wheel area. A PC computer and MED-PC software (Tatham and Zurn, 1989) controlled experimental events and data collection.

2.3. Procedure

Initially, 16 rats were shaped to lever press in standard, two-lever operant conditioning chambers. Each lever press earned a 10% sucrose solution. After two sessions, the sucrose concentration was decreased, and saccharin was gradually substituted for sucrose. In the final phase of this process, presses at one lever were reinforced with 0.25% saccharin, and presses at the other lever were reinforced with water, with side alternating between sessions. In the next phase of operant training, the contingencies were changed so that lever presses only occasionally produced a reinforcer eight sessions with a variable interval (VI) 5-s schedule and nine sessions with a variable ratio (VR) 5 schedule. Each session lasted 30 min, and sessions were typically run 7 days a week.

After operant lever-press training, the rats were placed in a free-turning wheel for 20-min sessions for 17 days. A "magazine training" (Iversen, 1993) procedure was then started. The session began with the wheel locked in place (brake on). A lever press or a 2-s period (whichever came first) unlocked the wheel for 1 min. In both cases the brake release was accompanied by a loud noise, and the lever was withdrawn from inside of the wheel. These conditions were in effect for three sessions. Next, the ratio requirement for wheel running was gradually increased from fixed-ratio 1 to fixed-ratio 8, while the running time was gradually decreased from 60 to 15 s. These changes took place over seven sessions. At this point, the eight rats with the highest bar-press rates were selected for the experiment.

In the final phase of training, the contingency was switched from ratio to variable interval. The interval values were increased from an average of 10 to 40 s over the course of seven sessions. For instance, in the final condition of training, lever presses earned 15-s access to a free-turning wheel according to a variable interval 40-s schedule. After 15 s of access (during which the rats ran, see below), the brake was reapplied and the lever was reinserted into the wheel. The next lever press started the interval timer, and the process began anew. Session length was 30 min.

2.3.1. Home-cage conditions, water phase

In the last phase of training, access to water was restricted to 1 h a day. The water bottle was placed in the home cage following the wheel-running session, along with the daily serving of chow (12–14 g). This condition, referred to as "pre-morphine" or "baseline", was in effect for 17 sessions (Sessions 1–17).

2.3.2. Morphine phase

Next, morphine sulphate (NIDA) plus saccharin was substituted for water in the home cage. The saccharin concentration was maintained at 0.25%. The initial morphine concentration was 0.2 mg/ml. Over the course of 12 days, concentration was increased in 0.1 mg/ml steps to 0.5 mg/ml. After 55 days, the amount of time the morphine bottle was kept in the home cage was increased from 1 to 3 h. Thus, there were 55 days in which the morphine access period was 1 h, and 14 days in which the access period was 3 h. Altogether, the rats drank morphine in the home cage for 69 successive days. During this phase, 56 wheel-running sessions were conducted (Sessions 18–73).

2.3.3. Saccharin phase

In the final condition, morphine was removed from the home-cage drinking solution. All other aspects of the procedure were kept the same. This last phase lasted for 15 sessions (Sessions 74–88).

2.3.4. Dependent measures

The number of lever presses, the number of reinforcers (opportunities to run in the wheel), the number of complete wheel revolutions (wheel-running responses), and the latency to the first lever press in each trial were recorded. Overall lever-press rate was defined in terms of intervals

during which the wheel was held by a brake, including the latency to the first lever-press response in each trial. Local lever-press rate was defined in terms of the period of time from the first, post-brake response (thereby, omitting the initial response latency). Fluid intake was measured on a 100-ml graduated cylinder after the remaining liquid in the cage bottle had been carefully transferred.

2.3.5. Statistical analysis

Repeated measures analysis of variance and paired *t* tests were used to analyze differences in fluid consumption, lever pressing, and wheel running. Trends for individual data were analyzed by the *C* statistic, a simplified time-series analysis, in which variability in successive data points is evaluated relative to changes in slope from one phase of the experiment to another (Tryon, 1982). This analysis yields a *Z* value on which significance tests are based.

3. Results

Since overall and local rates of responding were highly correlated ($r = .97$), results are reported only for the overall lever-press rates. Wheel-running rate (revolutions/minute) was also highly correlated with number of opportunities to run and total number of revolutions ($r = .87$ and .98, respectively). Thus, data on number of opportunities to run and on total number of revolutions are not reported here.

Fig. 1 shows liquid intake (milliliter/kilogram), morphine consumption (as measured in milligram/kilogram), lever-pressing rate, and wheel-running rate over the course of the experiment. The open data points indicate the first session of each condition, for example the introduction of morphine in Session 18 and the substitution of saccharin for morphine in Session 74. The filled data points are the average of three consecutive sessions, except for the last data point for each phase. The last data point is the average of the last two sessions of a condition.

3.1. Phase 1: water in home cage

3.1.1. Water consumption

Fig. 1A shows that water intake remained relatively stable over the entire first phase of the study (17 sessions). The average intake level over the last three sessions was 76.0 ml/kg (18.6 ml/rat). No morphine was available during this phase.

3.1.2. Lever pressing

Fig. 1C shows that lever-pressing rate remained relatively stable for the first 10 sessions and then increased to an average rate of approximately 17 responses/min from Sessions 11 to 17. A time-series analysis (Tryon, 1982) was applied to the data from the last eight sessions of this condition. The analysis confirmed the stability of the water baseline over these last sessions. In fact, no significant trend in response rates for any of the subjects was detected over these eight sessions ($Z < 1.64$ for every subject).

3.1.3. Wheel running

Fig. 1D shows average wheel-running rates, expressed in revolutions/minute. In the water phase, wheel running remained at about 35 rpm for the first four sessions, and then increased by about 30% to 45 turns/min and remained at this level for the remaining 13 sessions of this condition. The same time-series analysis as above was applied to the data from the last eight sessions of this condition. In seven out of the eight subjects, there was no evidence of a significant trend over these sessions ($Z < 1.64$), indicating stability of this response on this baseline phase. For the one exception, wheel running tended to decrease ($Z = 2.47$, $P < .01$).

3.2. Phase 2: morphine solution in home cage

3.2.1. Liquid consumption (volume)

Fig. 1A shows that fluid consumption decreased sharply on the first day that morphine was put in the home-cage bottle. Following this drop, fluid intake increased, and in a few days was back at the pre-morphine (water) level. With further exposure to morphine and increases in concentration (from 0.2 to 0.5 mg/ml), fluid consumption slightly increased, stabilizing at 80 ml/kg. Finally, there was a sizeable increase in morphine consumption when the time that the bottle was kept in the home cage was extended from 1 to 3 h (Session 60). For example, in the last two sessions of this condition, average intake was 135 ml/kg.

3.2.2. Morphine consumption (milligram/kilogram)

Fig. 1B shows morphine dose as measured in milligram/kilogram. This conversion is necessary in order to take into account the different concentrations during the first 12 sessions of this phase of the study. The data points are the same as in the top panel. Morphine consumption in the home cage increased from an average of 4 to 64 mg/kg of body weight over the first 20 days of self-administration. Consumption then stabilized at about 40 mg/kg. When the solution was made available for 3 h, a sharp increase in consumption occurred, reaching an average of 67 mg/kg on the last 2 days of this phase of the study. Day-to-day records indicate a trend toward greater between-session consistency. For example, the standard errors as measured across Sessions 19–21 and Sessions 72–73 decreased from 29.8% to 5.9%.

3.2.3. Lever pressing

Fig. 1C shows wheel-reinforced lever pressing rate. The first day of home cage morphine was followed by a 21% decrease in response rate (from 17 to 13.5 responses/min). However, responding soon recovered to the pre-morphine levels, and remained at about 17 responses/min even though

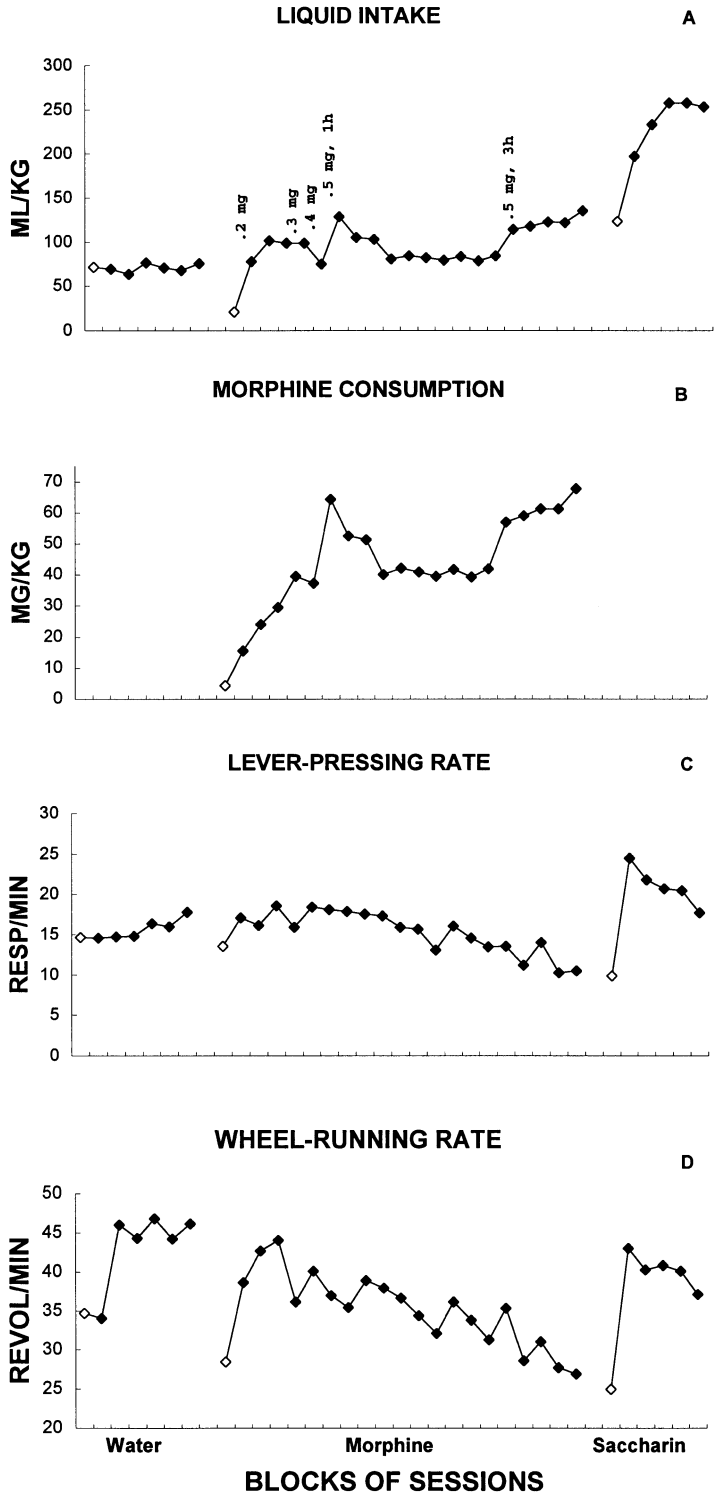

Fig. 1. The effect of morphine self-administration on wheel running and lever pressing for the opportunity to run. Data are shown for each daily session over the water, morphine, and saccharin phases. Panel A shows average liquid intake, in milliliter/kilogram; Panel B shows average morphine consumption, in milligram/kilogram, when a morphine solution was available in the home cage; Panel C shows average lever-pressing rate for the opportunity to run in the wheel; and Panel D shows average wheel-running rate. The open data points indicate the first session of each phase. The filled data points are the average of three consecutive sessions, except for the last data point for each phase. The last data point is the average of the last two sessions of a condition.

morphine concentration increased from 0.2 to 0.5 mg/ml. However, with continued exposure to morphine, wheel-reinforced lever pressing gradually declined. Starting from Session 41, 37 days after home-cage morphine drinking started, average response rate declined to a level of 11.7 responses/min in Session 73 (last session in this phase). This

downward trend was significant for six out of the eight subjects ($Z > 1.64$, $P < .05$ at least, for every subject). Thus, with continued exposure to morphine in the home cage, there was a decrease in wheel-reinforced lever pressing in the operant chambers. Moreover, this occurred even though 20–22 h separated morphine drinking and wheel running.

3.2.4. Wheel running

Fig. 1D shows that, following the first morphine session, average wheel-running rates decreased by about 35%, from 45 rpm on the last day of the water phase to 28 rpm on the first day of the morphine phase. But, as was the case with response rates, wheel running recovered to its prior level in just a few sessions. For instance, wheel-running rates ranged from 42 to 45 rpm over Days 5–9 of home-cage morphine consumption. However, starting at about Session 41, wheel running began to decline. For example, on the last session in which a 0.5 mg/ml-morphine solution was available for 1 h, the average wheel-running rate was 30.2 rpm, about 33% lower than the peak rate. The decreasing trend in wheel running was significant for seven out of the eight subjects ($Z > 1.64$, $P < .05$ at least). For the one exception, wheel running was too variable, with rates alternating in a range of 3.2–41.7 rpm ($Z = 0.60$).

The decline in wheel running and lever pressing was not accompanied by any apparent disabilities, such as repetitive head shakes or other stereotypic movements.

3.3. Phase 3: saccharin solution in home cage

3.3.1. Liquid consumption

In the third phase of the study, morphine was removed from the home cage bottle, so that it now served a 0.25% saccharin solution. On the first day of this condition, liquid consumption remained practically unchanged at 123.3 ml/kg. However, in subsequent sessions, liquid consumption increased, so that by the last two sessions of the experiment, the rats consumed an average of 254 ml/kg of 0.25% saccharin solution/session (see Fig. 1A).

In order to compare liquid intake among the home-cage water, morphine, and saccharin phases, the daily liquid intake was averaged across the last 3 days of each phase. A repeated measures ANOVA revealed a significant difference among these measures ($F_{(2,14)} = 85.81$, $P < .001$). Subsequent paired t tests revealed that the morphine solution intake was significantly higher than water intake ($t = 3.46$, $P < .01$) but lower than the saccharin solution consumption ($t = 8.06$, $P < .001$).

3.3.2. Lever pressing

On the first day after morphine was removed from the home-cage bottle, wheel-reinforced lever pressing remained at the morphine-induced depressed levels of about 10.5 responses/min. However, on Day 2 of home-cage saccharin, lever pressing increased by about 100% to an average level of 23.1 responses/min. This was the highest level observed in the study, some 35% higher than water baseline. In subsequent sessions, lever pressing rate began to decline. However, the decline was slow, and rates remained above baseline levels throughout. The downward trend was significant in three out of the eight subjects ($Z > 1.64$, $P < .05$). Among the other five subjects, three showed a nonsignificant decreasing trend ($Z = 1.02$, 0.73, and 0.75), one exhibited a practically constant rate ($Z = -0.05$), and one showed an increase followed by an incipient decrease in rate ($Z = 0.19$).

3.3.3. Wheel running

Fig. 1D shows that in the final, saccharin phase of the study, changes in wheel-running rates were similar to changes in lever-pressing rates. On the first saccharin day, wheel-running rates remained at the decreased levels that followed morphine consumption, about 25 rpm. However, on Days 2 and 3, wheel running increased to 38 and 46 rpm. Wheel running then began to decline. However, the downward trend was not significant in most subjects according to the C statistic. For two subjects, this statistic was significant ($Z = 1.99$ and 1.94, $P < .05$). The other subjects showed a nonsignificant decreasing trend ($Z = 1.11$,1.25, 1.27, and 1.41) or no clear tendency in wheel-running rates ($Z = -0.03$ and 0.19).

A one-way repeated measures ANOVA was conducted for the overall data presented on Fig. 1C and D, with the factor being blocks of sessions. The results indicated a significant effect for both lever-pressing ($F_{(33,231)} = 3.909$, $P < .001$) and wheel-running ($F_{(33,231)} = 8.700$, $P < .001$) rates. Pairwise comparisons were conducted between the mean for the last block of morphine sessions and the means for the last block of baseline sessions, the first saccharin session, the first block of saccharin sessions (saccharin days 2–4) and the last block of saccharin sessions. Lever-pressing mean for the last block of morphine sessions was significantly different from means for the last baseline sessions ($t = 2.83$, $P < .05$), for saccharin days 2–4 ($t = 4.92$, $P < .01$), and for the last saccharin sessions ($t = 3.31$, $P < .05$). Similarly, wheel-running mean for the last block of morphine sessions was significantly different from means for the last baseline sessions ($t = 4.73$, $P < .01$), for saccharin days 2–4 ($t = 5.23$, $P < .001$), and for the last saccharin sessions ($t = 3.84$, $P < .01$). The comparisons between the means for the last block of morphine sessions and for the first saccharin session were not significant either for lever-pressing ($t = 0.80$) or wheel-running ($t = 0.52$) rates.

Fig. 2 shows the percentage change in lever-pressing and wheel-running rates. The proportional scores were calculated relative to the last three sessions of the initial, water baseline. This way of presenting the results makes it easier to compare changes in lever pressing rate and wheel running rate. The statistical analysis of the proportional scores leads to the same conclusions as the analysis of the absolute rates: significant decreases in lever pressing and wheel running

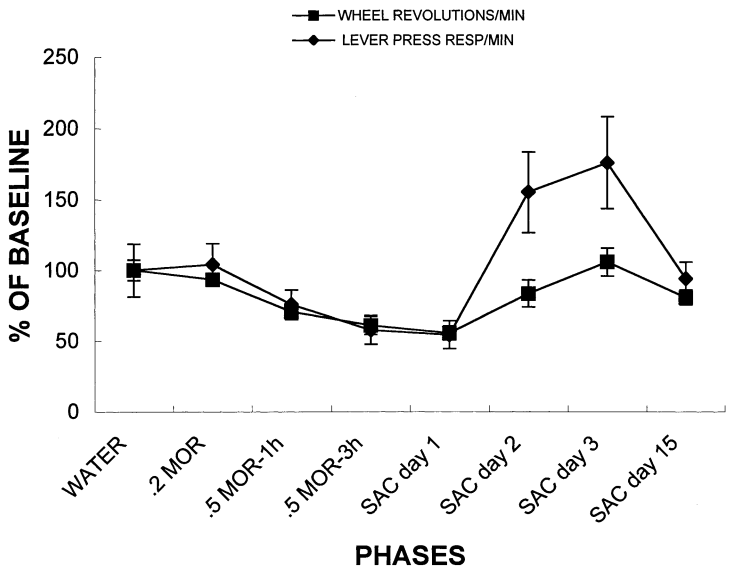

Fig. 2. Changes in wheel-reinforced lever-pressing rate and wheel-running speed in the morphine and post-morphine sessions. The proportional scores were calculated in terms of the rates in the last three sessions of the phase in which the home cage fluid was water. The data are shown as average and standard errors across the last three baseline water sessions, the last three sessions of morphine self-administration at 0.2 mg/ml (0.2 MOR), 0.5 mg/ml for 1 h (0.5 MOR-1 h) and 0.5 mg/ml for 3 h (0.5 MOR-3 h) concentrations, and Sessions 1, 2, 3, and 15 of saccharin in home cage.

following the introduction of morphine and return to baseline levels upon termination of morphine. In addition, the relative measures show that the changes in lever pressing after morphine termination were relatively larger than the changes in wheel running.

A repeated measures ANOVA yielded a significant phase effect ($F_{(7,49)}=6.286$, $P<.001$ for lever pressing; $F_{(7,49)}=7.541$, $P<.001$ for wheel running). Both the lever-pressing and the wheel-running percent rates decreased significantly below baseline levels on the last 3 days of morphine self-administration ($t=4.131$, $P<.01$ and 6.028, $P<.001$, respectively; paired t tests). This tendency towards a reduced rate was still present on the first day of withdrawal ($t=4.6$, $P<.01$ and 8.991, $P<.001$, respectively). However, it was reversed on the second and third days of withdrawal, when the proportion of both lever-pressing and wheel-running rates reached values similar or higher than the baseline rates, and thus well above the final morphine level. This reversal was significantly more pronounced for lever pressing than for wheel running. In fact, pairwise comparisons confirmed that the clear tendency portrayed in Fig. 2 was due to lever-pressing rates being higher than wheel-running rates on saccharin days 2 and 3 ($t=2.55$, $P<.05$ and $t=2.86$, $P<.05$, respectively). This difference was still present on saccharin days 5, 7, and 8 ($t=2.40$, 2.64, and 2.90, $P<.05$).

3.3.4. Weight and health conditions

The average weights of the animals increased from 248 g at the end of baseline to 272 g at the end of the morphine phase ($t=6.71$, $P<.001$), and to 283 g at the end of the saccharin phase ($t=5.23$, $P<.01$, for Morphine × Saccharin). Thus, the morphine self-administration regimen did not cause weight loss either during the morphine phase or upon drug removal. Occasional diarrhea, but no signs of distress, irritability, or difficulty in handling were observed when rats were placed on the wheel apparatus at any time during the experiment. Thus, the rats appeared to remain healthy throughout the experiment.

4. Discussion

The major findings were that (1) chronic morphine consumption was accompanied by a decrease in wheel-running rate and wheel running-reinforced lever pressing, (2) that the termination of morphine consumption resulted in increases in both wheel running and lever pressing to levels that were similar or higher than the original baseline levels, (3) that the post-morphine increase in lever pressing was substantially larger than the post-morphine increase in wheel running, and (4) that the rebound in lever pressing and wheel running was not immediate, but took one session. That is, the first session that followed home-cage saccharin consumption looked like the previous post-morphine sessions.

Before considering the mechanisms that may have mediated the relationship between morphine consumption and changes in lever pressing and wheel running, it would be useful to consider factors that might limit the generality of the findings. The two most obvious methodological limitations were that the rats were selected from a group of 16 on the basis of lever press rates and food was restricted. The rationale for both procedures was to insure robust wheel running. For instance, wheel running is much more likely in rats that do not have free access to food (Belke and Heyman,

1994). However, to our knowledge, there is no evidence that activity level or factors associated with food intake mediate morphine's influence on lever pressing or wheel running. Also, it should be pointed out that the level of restriction was moderate in that the subjects gained weight, about 5 g a month, throughout the course of the study. Thus, the generality of the findings are not likely to be constrained by the feeding regime or choice of subjects.

The study was motivated by the hypothesis that morphine consumption would lead to a decrease in wheel running, and, in particular, a decrease in the reinforcing value of wheel running. Wheel running decreased, as predicted. However, the decrease could have been due to a general decrease in the capacity to respond or due to a decrease in both performance and reward value. We will consider each hypothesis in turn.

If morphine consumption led to a general motor deficit, then the simplest expectation is that relative changes in lever pressing and wheel running would be similar. For example, a general slowing of behavior would result in equivalent proportionate decreases. Fig. 2 shows that the relative declines were virtually identical, as predicted. However, the rebound effect for lever pressing was considerably larger. This suggests that changes in motor performance, if present, were not the only consequence of chronic morphine consumption.

If morphine consumption led to a decrease in the rewarding efficacy of wheel running, then the simplest expectation is that lever-pressing rates should change more than wheel-running rates. For example, imagine that a given level of wheel running is now half as rewarding as it was prior to morphine and that wheel running itself decreased by 50%. All else being equal, the reward value of wheel running now is one-quarter of its original value. However, lever pressing decreased no more than did wheel running, suggesting a given level of wheel running maintained its prior reward value.

Finally, if there were changes in motor performance and the rewarding power of wheel running, there should be differential changes in lever pressing and wheel running throughout the study, but to a lesser degree than if there were only a reward effect.

The changes in responding in those sessions that followed morphine consumption are more in line with the hypotheses that (1) morphine consumption led to a general decline in performance and (2) there was no change in the reward value of wheel running. Possibly, then, the decreases in responding were symptomatic of an opiate withdrawal state. For instance, morphine consumption levels were high, and the rats had been without morphine for 20 or more hours. But, as noted above, a performance-based account leaves unexplained the post-morphine increase in lever pressing.

The uncertainty about the mechanisms that mediated morphine-related changes in lever pressing and wheel running should not, however, obscure the main findings. As predicted, morphine consumption led to decreases in instrumental activities, even though these decreases occurred some 20 or more hours after the drug consumption period. This suggests that chronic opiate consumption elicited residual adaptations that undermined the capacity to perform coordinated motor activities. It would be of interest to know if there is a similar phenomenon in chronic human opiate consumption, and if so, if it indirectly increases preference for opiates.

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