Psychopharmacology 60, 165–172 (1979)

Psychopharmacology

Effects of Morphine Withdrawal on Food Competition Hierarchies and Fighting Behavior in Rats*

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Abstract. The effects of chronic morphine administration and morphine withdrawal on competitive and fighting behaviors in rats were studied in a novel paradigm. Fixed-ratio 20 (FR-20) lever-pressing for food presentation was stabilized before placing pairs of rats, matched by response rate and body weight, in the behavioral testing chambers. Initially, overt fighting occurred, but in 60% of the pairs it dissipated within several sessions, accompanied by the development of stable dominant-submissive responding hierarchies. Invariably, the dominant rat in the initial fighting bouts became the dominant responding rat. Chronic morphine administration and subsequent withdrawal in one or both members of the pairs led to disruptions or reversals in the distribution of responding and to small increases in fighting. These effects were seen as early as 12 h after the second dose of morphine and, in some pairs, lasted at least 28 days after morphine was withdrawn. The results from experiments in which only one rat was made dependent show that both the withdrawn dominant rats and the withdrawn submissive rats contributed to the behavioral changes observed in the pairs during withdrawal. Differential food deprivation in pairs not exposed to morphine did not change the dominant-submissive hierarchies. Significant changes in the distribution of FR-20 responding in the paired condition were evident after FR-20 responding in the unpaired condition returned to control rates. It is therefore concluded that change in so-called appetite for food is not an important determinant of the hierarchical changes observed during protracted withdrawal.

Key words: Morphine withdrawal – Aggression – Competition – Hierarchies – Fighting

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Withdrawal from chronic morphine administration has been associated with an increase in fighting behavior in rats (Boshka et al., 1966; Davis and Khalsa, 1971; Lal et al., 1971) and monkeys (Villarreal, 1973). The observation that fighting bouts were usually precipitated by contact between the participants (Thor and Teel, 1968; Villarreal, 1973) suggests that the increase in fighting is related to the hyperirritable state of the withdrawn animals (Himmelsbach et al., 1935; Villarreal, 1973; Grumbach et al., 1974). Also, the increase in shock-elicited fighting (Ulrich and Azrin, 1962) reported for withdrawn rats (Davis and Khalsa, 1971; Puri and Lal, 1974) may be related to the reduced threshold for the 'flinch-jump' reaction to electric shock (hyperalgesia) seen in this species during withdrawal (Tilson et al., 1973). These descriptions suggest that the fighting behaviors observed during morphine withdrawal fall within the category of irritable or pain-elicited aggression (Ulrich, 1966; Moyer, 1968). This type of aggressive behavior occurs in response to noxious stimuli, lacks ritualized fighting postures, and is directed toward any attackable organism or object.

Morphine withdrawal may induce other forms of aggressive behaviors in the rat that are behaviorally and physiologically distinct from irritable-type aggression (Moyer, 1968; Eichelman and Thoa, 1973). The experiments described in this report were designed to determine if some of the fighting observed among morphine-withdrawn rats is related to intraspecific aggression. This type of aggressive behavior generally occurs between male rats and is easily identified by the appearance and sequence of threat and submissive postures that precede and follow actual fighting; indeed, these postures may preempt actual fighting (Grant and Mackintosh, 1963; Miczek, 1974).

The behaviors of the rats were studied in an operant competitive paradigm because it has previously been shown that competition for food induces spontaneous aggression in this species (Miczek, 1974; Zook and

0033-3158/79/0060/0165/$01.60

Adams, 1975). Food-deprived rats were trained in an operant chamber to press a lever on a fixed-ratio (FR-20) schedule to obtain food pellets. After their behavior had stabilized they were placed in the chamber in matched pairs and relative frequencies of lever-pressing and fighting behavior between the members of the pairs were monitored before, during, and after chronic morphine injections.

Materials and Methods

Subjects. Male, Long-Evans hooded rats obtained from Blue-Spruce Farms (Altamount, New York) at 2.0–2.5 months of age (about 300 g) served as subjects for all experiments. Upon arrival, they were housed for 1–2 weeks in community cages, six to a cage, in a constant environment room with 12-h light-dark cycles. They were then placed into individual cages until their body weights reached 350–400 g, after which they were food deprived until they reached 80% of their free-feeding weights. The rats were maintained at this weight by restricting their total daily food intake to 20–25 g of either Purina Rat Chow or combination of rat chow and food pellets earned in the operant test chamber. During withdrawal from morphine the rats typically lost weight; therefore, they were given additional chow equal in weight to half the difference between the animals' actual weight and 80% free-feeding weight. Water was freely available at all times in the home cages.

Apparatus. All behavioral experiments were conducted in standard behavioral testing chambers housed in sound-attenuating enclosures equipped with ventilating fans. On one wall of the 25 cm × 27 cm × 36 cm chamber were two levers, one of which required a weight of 15 g to activate, stimulus lights, and a food-pellet delivery trough. A stimulus light above the active lever was illuminated during the behavioral sessions. Fixed-ratio (FR) schedules of food-pellet (Noyes, Lancaster, New Hampshire) delivery were programmed and data recorded by standard electro-mechanical equipment located in an adjacent room.

Procedure for Evaluating Fighting and Competitive Behaviors. The rats were trained to press a lever (respond) under an FR-20 schedule of food presentation (every 20th response was followed by delivery of a 45-mg food pellet). The left lever was operative for half of the rats; the right lever had no programmed consequences. The other rats were required to press the right lever for food pellets. After responding had stabilized (3–4 weeks after training had begun), pairs of rats were formed by matching both the rates of responding on the same lever and body weights of the individual rats within 10% of each other. The operant and fighting behaviors of the paired rats in the test chamber were monitored during 15-min sessions by closed circuit television and, initially, tape recorded to allow repeated analyses. The amount of time that each rat of a pair was responding and that both rats were engaged in fighting behavior was recorded by manually closing switches of timing devices (running-time meters, 5 pulses/s) for the duration each behavior was observed.

Aggression or fighting was defined as occurring when both members of a pair engaged in one of three behaviors: upright defensive (boxing) postures; actual wrestling, squealing, and biting; and dominant-submissive postures(submissive rat on its back or side with the dominant rat hovering over it, usually resting its forepaws on the submissive rat). These behaviors have been well-defined and illustrated by Grant and Mackintosh (1963) and usually occur in the above sequence. Miczek (1974) has used similar behaviors to evaluate aggressive encounters in rats and found the correlation coefficients for interobserver and intraobserver reliability to range consistently between 0.88 and 0.98. When the video tapes of the fighting and responding behaviors monitored here were reevaluated blind, the intraobserver scores never differed by more than 10%.

Table 1. Schedule of morphine injections and behavioral testing sessions

Day	Morphine dose (mg/kg, i.p.)	Test condition
1	2×25	–
2	2×25	unpaired
3	2×50	paired
4	2×50	unpaired
5	2×75	paired
6	2×75	unpaired[a]
7	2×100	paired[a]
8	2×100	unpaired
9	100	paired[b]

[a] During the first experiment, in which both rats were injected with morphine, behavior was not monitored on days 6 and 7

[b] Two paired sessions were conducted during the first experiments. The first session was run prior to their morning injection; the second session was run 6 h later

Effects of Repeated Morphine Injections and Withdrawal: Both Rats of Each Pair Given Morphine. Four pairs of rats with stable responding hierarchies (pairs in which one rat controlled the response lever over 80% of the session over four consecutive sessions – see Results) were given repeated morphine injections every 12 h for nine days and then withdrawn. Both members of each pair were given four i.p. injections of 25, 50, and 75 mg morphine/kg and five injections of 100 mg/kg. All behavioral sessions lasted 15 min. On the second day of the experiment each rat was placed individually into an operant chamber for a 15-min session immediately prior to receiving its third morphine injection (25 mg/kg). The next morning the rats were placed in pairs into the operant chambers for 15-min sessions prior to their first 50 mg/kg injection of morphine. Therefore, on alternate days rats were placed into operant chambers alone (unpaired) or paired to determine the effects of chronic morphine injections upon FR-20 behavior. See Table 1 for the schedule of morphine injections and behavioral testing sessions. The fighting and lever-pressing behaviors of the paired rats were monitored during 15-min sessions 1–6, 9, 14, and 28 days after termination of the morphine injections. Response rates of the unpaired rats were also determined over the first 6 days of withdrawal, during 15-min sessions 1–2 h after their behaviors in the paired condition were monitored. We observed what appeared to be a dose-dependent alteration in behavior 12 h after morphine administration, immediately prior to the next scheduled injection. In addition, they seemed to be a little more irritable upon handling and showed other subtle signs of withdrawal (loose or soft fecal pellets). To determine if the measured behavioral effects were due to cumulation of the opiate or to abstinence, we administered a 5th dose of 100 mg morphine/kg on the 9th day and monitored paired behavior 6 h later. We reasoned that if cumulation of morphine were responsible for the behavioral changes, there should be a greater effect 6 h after drug, compared with changes seen 12 h after drug. Alternatively, if 12 h between injections were adequate to induce dependence and abstinence, we expected to see less of a behavioral effect, or none at all when tested 6 h after morphine.

Dominant or Submissive Members Given Morphine Injections. Seven pairs of rats were used in the first series of experiments. The submissive (nonresponding – vide infra) members of four pairs and the dominant (responding) members of three pairs were given morphine injections, while their partners received saline injections on the same schedule used in the previous experiments. Two months after the completion of this series of experiments, the second series was begun. The dominant members of four pairs and submissive members of three pairs were given repeated morphine injections and withdrawn. Four pairs of rats used in the first series were again used in the second series, but the morphine and saline injections were reversed in each pair. Behaviors emitted by the paired and unpaired rats during the period of morphine injections were monitored at the same times as in the previous experiment (Table 1), with additional testing sessions conducted between 10 a.m. and 12 noon on the 6th day (unpaired) and the 7th day (paired) of treatment. During withdrawal, behaviors of the paired rats, and several hours later, responding by the individual rats, were monitored 1 – 7, 10, 14, 18, 21, 24, and 28 days after the last injection of morphine. In these experiments, the distribution of responding within pairs was evaluated by recording the actual number of responses emitted by each member, in addition to determining the amount of time overt fighting was observed during the 15-min sessions.

Statistical Analysis. The relatively small day-to-day intrasubject variability afforded by stable, operant behavior, in both the unpaired and paired condition, allowed us to use each subject as its own control. In this way we could statistically analyze, fairly objectively, behavior which otherwise would be difficult to study. Having established that the winners of initial aggressive encounters invariably became what we defined as the dominant members of competing pairs, we chose to study the effect of drug treatment on the operant response in the unpaired condition. We reasoned that changes in agonistic or aggressive behaviors should alter the level of individual responding in the paired condition. However, if either or both of the members of the competing pairs were physically incapable of responding, or if the treatment interacted with the food deprivation, which was used to maintain responding, changes in paired responding might also be altered. If such were the case, it would be impossible to conclude that changes in the social dynamics, which maintained the hierarchies, were responsible for changes in the distribution of responding. The effects of chronic morphine administration and withdrawal on the complex behavior studied in these experiments showed great variability in both magnitude and temporal patterning for the group as a whole. Therefore, two-way analyses of variance for repeated measures and Student's t-test for paired (against each subject's control values) observations were used for statistical evaluation of the data. Treatment effects that gave P values of less than 5% were considered significant.

Drugs. Morphine sulfate was obtained from Merck and Company, Rahway, New Jersey. It was dissolved in 0.9% saline in appropriate concentrations so that all doses were given i.p. in a volume of 1 or 2 ml/kg. All doses are expressed as the salt.

Results

Formation of Competition Hierarchies. Seventeen of the 28 pairs initially tested in the competition paradigm formed stable dominant-submissive hierarchies. During the first two or three (15-min) sessions the rats were paired, there was much struggling between the rats, i.e., pushing, crawling over one another, etc., to get at the response lever; this often led to overt fighting behavior. Overt fighting was, however, highly variable among the pairs. The median amount of time engaged in this behavior was 9.5 s/15-min session (range: 0 – 368 s) for the 17 pairs of rats during the first session they were paired. By the fifth session an average of only 0.4 s (range: 0 – 5 s) of fighting was recorded. A total of 21 fighting bouts occurred over the first 5 sessions in which a winning rat could be determined. The winner was judged to be the rat in the dominant position at the end of the fight.

The rats that were clearly dominant in 20 of the 21 fighting bouts observed during five sessions also became the rats controlling the response lever for at least 80% of the fifth session. These rats will hereafter be referred to as the dominant rats. The submissive members of the pairs would occasionally try to get to the response lever or food trough, which resulted in threat behavior by the dominant rat or which precipitated short fighting episodes. The hierarchies were considered stable if the dominant rat maintained control of the response lever more than 80% of the session over four consecutive sessions. Although this criterion was arbitrarily set by us, the dominant rat typically emitted 98 – 100% of the total lever-presses each session and ate all of the food pellets it earned.

Effects of Repeated Morphine Injections and Withdrawal on Behavior: Both Members of the Pairs Treated. Behavior of the rats in the unpaired or paired condition was monitored 12 h after the second or fourth morphine injection, respectively, of 25, 50, and 100 mg/kg (see Table 1). There was an overall significant effect of chronic morphine treatment upon behavior of all 8 rats in the unpaired condition ($F_{3,21} = 5.918$, $P < 0.005$). Additionally, control of the lever by the dominant rats was significantly diminished ($F_{7,21} = 3.279$, $P < 0.02$), while a significant increase in the amount of time the submissive rats controlled the lever was observed ($F_{7,21} = 4.248$, $P < 0.005$). As seen in Table 2, the change in paired FR-20 responding was dose-related, but unpaired responding was significantly suppressed within 1 day of initiating morphine injections. Although it was observed 12 h after the second injection of 25 mg morphine/kg, it is possible that cumulative or residual effects of the relatively high doses of opiate could have been responsible. However, the fact that submissive rats showed increased control of the lever during the paired condition, coupled with the occasional appearance of subtle signs of withdrawal before their next injection (12 h apart), suggested that this injection schedule was capable of inducing tolerance/dependence of a magnitude great enough to render the subjects withdrawn during the period we (and others) defined as one of chronic morphinization. The second alternative proved to be the case. When paired behavior was monitored 6 h after their fifth injection of 100 mg morphine/kg, the response distribution between dominant and submissive members was virtually identical to that observed during the four control sessions immedia-

Table 2. Effect of escalating doses of morphine, administered every 12 h, upon responding by rats in the unpaired and paired conditions[a]

Morphine SO_4 (mg/kg, i.p.)	Unpaired FR-20 behavior (responses/ 15 min)	Control of lever (s/15 min)	
		Dominant rats	submissive rats
Saline	1861 ± 48	704 ± 22	10 ± 1
25	1502 ± 84**	750 ± 25	12 ± 7
50	1504 ± 104**	605 ± 86	86 ± 47
100	1458 ± 114	465 ± 117	241 ± 90*
100 (6 h)	–	713 ± 36	3 ± 3

[a] Unpaired behavior was monitored 12 h after the second and paired behavior was monitored 12 h after the fourth injection of morphine sulfate, at the doses indicated (see Table 1 for schedule of treatment and behavior sessions). Behavior was not monitored after 75 mg/kg. The last paired session was run 6 h after 100 mg/kg, which was injected immediately after the paired session run 12 h after their fourth morphine injection at this dose level. Values represent the mean (± SEM) of responses emitted per 15-min session in the unpaired condition ($N = 8$) or mean (± SEM) seconds in control of the operant lever per 15-min session in the paired condition ($N = N = 4$). The values for the saline control were derived by averaging data from 4 sessions

* $P < 0.05$

** $P < 0.01$ (Student's two-tailed paired t-test, using each subject's own saline control data)

Table 3. Suppression of unpaired and differential alteration of paired behavior in rats withdrawn from morphine[a]

Days into withdrawal	Unpaired FR-20 behavior (Responses/ 15 min)	Dominant rats	Submissive rats
1	979 ± 146**	209 ± 104*	268 ± 160
2	1443 ± 82**	184 ± 95*	238 ± 114*
3	1898 ± 81	337 ± 84*	354 ± 102*
4	2000 ± 101	317 ± 89*	258 ± 78*
5	1917 ± 156	496 ± 116	134 ± 61
6	1994 ± 94	625 ± 83	54 ± 28
9	–	600 ± 31*	108 ± 26**
14	–	755 ± 61	1 ± 0
28	–	744 ± 61	4 ± 2

[a] Rats were administered increasing doses of morphine sulfate twice a day (see Table 1) and exposed to unpaired and paired behavioral sessions 12 h after drug, immediately prior to their next injection (see Table 2). One to six days after their last injection they were run in the paired condition (10 a.m. – 12 noon) and 1 – 2 h later in the unpaired condition. Additionally, paired behavior was monitored on days 9, 14, and 28 of withdrawal. Values represent the mean (± SEM) of responses emitted per 15-min session in the unpaired condition ($N = 6$) or mean (± SEM) seconds in control of the operant lever for 15-min session in the paired condition ($N = N = 3$)

* $P < 0.05$

** $P < 0.01$ (Student's two-tailed paired t-test using each subject's own saline control data, e.g., Table 2)

tely prior to initiating morphine treatment (Table 2). Fighting behavior was not very apparent (7.5 ± 1.2 s, M ± SEM) during control sessions. There was a small but nonsignificant decrease in this behavior during chronic morphine treatment. Perhaps this trend was not statistically reliable because of the low basal level of fighting among established pairs.

No additional morphine was given and the behaviors of three pairs of rats were monitored through the 28th day of abstinence. The established hierarchies of the three pairs broke down during the first 6 days into withdrawal. The submissive rat of each of the three pairs became dominant on the response lever during at least one of the sessions conducted at this time. Prolonged fighting episodes (range: 25 – 75 s) were observed in two of the pairs during these sessions. By the 14th day of abstinence the original dominant rats resumed total control of the response lever and food trough while fighting disappeared, except for sporadic episodes, similar to that noted during premorphine control sessions. As a group, significant decreases in control of the lever by the dominant rat were observed during the first 4 days into withdrawal. By the 6th day, the hierarchies appeared to have restabilized, but on the 9th day a small but significant decrease in control of the lever was recorded for the dominant rats. The submissive rats, while presumably equally dependent and withdrawn, showed an effect opposite to that seen in the dominant group. Control of the lever went from 10 s/15-min session (Table 2) to over 200 s on the 1st and 2nd days into withdrawal, remaining significantly elevated through the 4th day. A reemergence of a significant increase in the amount of time the submissive rats controlled the lever was evident on the 9th day of withdrawal. While unpaired responding was also compromised by the withdrawal state, the effect was short-lived. Responding returned to control rates by the 3rd day into withdrawal (Table 3). Because overt fighting behavior was highly variable from day to day, analysis of this behavior did not result in a statistically reliable outcome.

Dominant Morphine-Treated Members. Recording the number of responses emitted by the rats in the paired condition gave indications of drug- or withdrawal-induced changes in the hierarchies, which were interpreted in a manner identical to that obtained by recording time in control of the response lever. However, responses emitted in the paired condition are shown in Tables 4 and 5, so that paired responding can be directly compared and contrasted with responding in the unpaired condition.

Two-way analyses of variance of paired responding, throughout the course of morphine treatment and withdrawal, showed overall significant effects for both

Table 4. Effect of repeated morphine injections and withdrawal on responding by the rats in the paired and unpaired conditions and on fighting behavior: dominant rats given morphine, submissive rats given saline

Period		Control	Morphine treatment	1–3 Days	4–6 Days	7–14 Days	21–28 Days
Responses emitted by paired:	Dom rats	4419 ± 357[a]	3026 ± 304*	2182 ± 493*	3529 ± 448	2915 ± 747	2865 ± 998
	Sub rats	5 ± 5	302 ± 143***	500 ± 119****	261 ± 160***	322 ± 134****	1336 ± 654**
Seconds of fighting		4.6 ± 1.2[b]	2.5 ± 1.0	45 ± 21*	10 ± 3.6	34 ± 16	3.7 ± 1.1
Responses emitted by unpaired:	Dom rats	5780 ± 223	3726 ± 304****	3682 ± 221****	5373 ± 218	5669 ± 305	–
	Sub rats	5580 ± 234	5169 ± 231	5601 ± 278	5469 ± 320	5394 ± 217	–

[a] Mean (± SEM) responses emitted by the paired or unpaired dominant (Dom) and submissive (Sub) rats ($N = 7$)

[b] Mean (± SEM) seconds of fighting behavior by the paired rats ($N = 7$). The means shown for the behaviors were obtained by summing the responses emitted by the rats in the paired or unpaired conditions or the seconds of fighting by the paired rats over 3 consecutive sessions for each period shown. The control data are from three consecutive sessions (paired and unpaired rats) which immediately preceded initiation of morphine injections. The morphine-treatment data are from paired rat sessions conducted on the 5th, 7th, and 9th days of morphine injections; the unpaired response rates are from sessions conducted on the 4th, 6th, and 8th days of morphine injections (see Table 1). The data shown for the four withdrawal periods are from sessions conducted with the rats, first in the paired condition and, several hours later, in the unpaired condition 1, 2, and 3 days; 4, 5, and 6 days; 7, 10, and 14 days; and 21, 24, and 28 days after morphine injections were terminated

* $P < 0.05$

** $P < 0.02$

*** $P < 0.01$

**** $P < 0.001$, when compared with control (Student's two-tailed t-test for paired observations)

Table 5. Effects of repeated morphine injections and withdrawal on responding by rats in the paired and unpaired conditions and on fighting behavior: dominant rats given saline, submissive rats given morphine

Period		Control	Morphine treatment	Withdrawal (days after last injection)			
				1–3 Days	4–6 Days	7–14 Days	21–28 Days
Responses emitted by paired:	Dom rats	4203 ± 404[a]	3618 ± 611	3839 ± 644	2639 ± 501*	3660 ± 429	4378 ± 488
	Sub rats	22 ± 17[a]	84 ± 38	314 ± 207	846 ± 574	363 ± 214	89 ± 84
Seconds of fighting		3.7 ± 0.9[b]	1.4 ± 0.6	12 ± 3.5*	9.7 ± 4.1	8.0 ± 3.8	2.5 ± 0.8
Responses emitted by unpaired:	Dom rats	5762 ± 285	5441 ± 320	5732 ± 412	5565 ± 344	5683 ± 313	–
	Sub rats	5636 ± 312	3523 ± 566**	3754 ± 541***	5370 ± 323	5817 ± 365	–

[a] Mean (± SEM) of the responses emitted by the paired or unpaired dominant (Dom) and submissive (Sub) rats ($N = 7$)

[b] Mean (± SEM) seconds of fighting behavior by the paired rats ($N = 7$). The means shown for the behaviors were obtained by summing the responses emitted by the rats in the paired or unpaired conditions or the seconds of fighting by the paired rats over 3 consecutive sessions for each period shown. (See legend of Table 4)

* $P < 0.05$

** $P < 0.01$

*** $P < 0.001$, when compared with control (Student's two-tailed t-test for paired observations)

the treated dominant rats ($F_{5,30} = 3.449$, $P < 0.02$) and the untreated submissive rats ($F_{5,30} = 3.966$, $P < 0.01$). In the unpaired condition, only the dominant group showed an overall treatment effect that was highly significant ($F_{4,24} = 24.007$, $P < 0.001$). Throughout the course of treatment and withdrawal of the dominant rats, responding by the submissive rats increased dramatically when in the paired condition and remained significantly increased for as long as they were studied (up to 28 days into withdrawal).

However, the significant suppression of unpaired responding by the treated, dominant rats gave way and returned to control rates within 4–6 days after discontinuing morphine injections. A significant treatment effect upon fighting behavior was also observed ($F_{5,30} = 4.395$, $P < 0.005$). This was due to a significant increase in the amount of time spent on this behavior during the first 3 days into withdrawal (Table 4). Examination of data from individual pairs indicated that during the 2nd week of withdrawal reversals or disruptions of the hierarchies occurred in 4 of the 7 pairs. This redistribution of paired responding, which was accompanied by a recurrence of fighting episodes in these pairs (range: 20–79 s) was reminiscent of observations made during the first experiment in which both members were made dependent and withdrawn. Three of the hierarchies remained reversed through the 4th week of withdrawal, but little fighting was observed in any of the 7 pairs after the 2nd week of withdrawal.

Submissive Morphine-Treated Members. Although treatment of the submissive rats produced an effect upon paired responding in this group that only approached statistical reliability ($F_{5,30} = 2.096$, $P < 0.1$), the overall effect upon responding by the untreated, dominant rats was significant ($F_{5,30} = 2.974$, $P < 0.05$). Like the unpaired behavior of the rats in the previous experiment, only the treated group (submissive rats in this case) showed an overall significant effect ($F_{4,24} = 22.561$, $P < 0.001$). The suppression of unpaired behavior occurred during the course of morphine treatment and during the first 3 days of withdrawal (Table 5). It was also during the first 3 days of withdrawal that fighting increased significantly ($F_{5,30} = 3.169$, $P < 0.02$) as well. However, the most dramatic effect upon paired responding occurred between 4–6 days into withdrawal. During this time, behavior of the untreated dominant rats was significantly suppressed, even though the increase in responding by the withdrawn, submissive rats was highly variable and not statistically reliable (Table 5). Disruptions were observed in three pairs, and a complete reversal occurred in a fourth pair during this period of withdrawal. Only 3 pairs displayed some fighting episodes at this time (range: 6–14 s). Very little fighting was observed past the second week of abstinence, and all hierarchies had reverted to premorphine control conditions by the 4th week of abstinence.

Lack of Effect of Differential Food Deprivation on the Behaviors of Paired Rats. The rats withdrawn from morphine lost an average of 11% in body weight (baseline weights were already 80% of free-feeding weights), regardless of hierarchical position occupied. Some of the increased responding in the paired condition by the withdrawn submissive rats could have been due to relatively greater food deprivation in this member compared to their nonwithdrawn dominant partners. Therefore, the effects of differential food deprivation in five nondependent pairs of competing rats were studied to determine if the weight loss due to morphine withdrawal contributed to the increased paired responding by the submissive rats. Submissive rats of five stable pairs were food-deprived first to 75% and then to 70% of their free-feeding weights, while their dominant partners remained at 80% of free-feeding weights. They were tested at each deprivation level, but no changes in the distribution of responding or fighting behavior were observed. Increasing the body weights of the dominant rats to 85%, while the submissive members remained at 70%, also had no effect on the distribution of paired behavior.

Discussion

Several factors prompted us to try to develop a different method for studying the consequences of withdrawal upon so-called aggressive behavior in rats. Although shock-elicited fighting had previously been reported to be increased during withdrawal from opiates (Davis and Khalsa, 1971; Puri and Lal, 1974), the interaction of shock with the lowered threshold to noxious stimuli during withdrawal (Tilson et al., 1973) made interpretation of results of this kind difficult. For example, withdrawal would result in perception of shock (whose physical characteristics were unchanged by the experimenter) as being more intense. At one level of analysis, increased fighting in response to shock could be considered evidence for increased aggressiveness. However, if morphine-naive rats were exposed to greater shock intensities, which they perceived as equally noxious to the milder shock given the withdrawn rats, fighting would surely increase in the drug-naive group. Since we were interested in determining if other than 'irritable' or 'pain-elicited' aggression emerged during withdrawal from morphine, we deemed the above models inappropriate. Furthermore, we observed (as countless others have) that overt, easily quantifiable fighting behaviors were highly variable and rapidly dissipated when male members of this species were paired or grouped. One option was to learn to discriminate (and to interpret) the many postures and behaviors described in the ethological literature, and then to spend several years determining if drugs altered the 'tendency' or 'willingness' to engage in the varied behaviors or just incapacitated the animals so they were incapable of engaging in the behavior, even though they might be 'willing' to do so. These factors become important if one is interested in drugging limited members of groups of subjects, one or more of which may be pivotal in maintaining order within the group (vide infra). Finally, to embrace and utilize a type of behavioral analysis that depends to such a great extent upon the use of theoretical constructs was contrary to the operant analyses we have used so extensively in the past to study effects of drugs upon biochemistry and behavior.

Although we have observed some statistically reliable increases in overt fighting behavior among pairs of rats in which one member was treated with morphine and withdrawn, the episodes were sporadic and variable. We were impressed with the more dependable measure of operant behavior, whether determined as time controlling the lever or actual responses emitted.

The advantages of using competition for the opportunity to lever-press in an operant setting to study aggressive behavior were several: (1) stable behavioral baselines were established before beginning drug treatment and, in most cases, were reestablished after withdrawal had run its course, allowing each subject to serve as its own control; (2) dominant and submissive rats were readily identifiable in each pair; (3) the high-response requirement for food-pellet delivery allowed extended observation of the competition behavior of the pairs, thus enabling us to evaluate both the magnitude and the quality of the withdrawal-induced changes in aggressive behavior.

The fighting episodes observed during withdrawal were very often associated with changes in the distribution of lever-pressing between the members of the competing pairs. This, plus the observation that the rats dominant in the fighting episodes that occurred during formation of the hierarchies also became the dominant responding members, suggests that the breakdowns in the responding hierarchies and the increases in fighting behavior were interrelated. The various postures that maintain dominance and submission in fighting may also maintain these roles in other forms of social behavior. Thus, a more sensitive and objective indicator of subtle changes in aggressive behaviors in this particular paradigm may be the changes in distribution of responding rather than just the appearance of overt fighting postures within pairs of rats. Gottier (1972) has stated that aggressive behavior is an "overall process which is not readily observed as a well-developed dominance hierarchy in mature organisms." Thus, a change in a dominance hierarchy may reflect subtle or overt changes in aggressive behavior among the individuals comprising the hierarchy.

The increased fighting during morphine withdrawal may, in part, have been related to irritable (pain-elicited) aggression (Ulrich, 1966; Moyer, 1968; Eichelman and Thoa, 1973) due to the hyperalgesic, hyperirritable state of the rats. However, the withdrawal state may also have caused loss of behavioral control by the cue complex of the partner (threat postures, submissive postures, etc.) and social position, which led to the breakdown of the established hierarchies and the increased fighting. The cue complex of the dominant rats, which normally maintained very low rates of responding by their submissive partners, may no longer have been attended to by the submissive rats when they were withdrawn. Additionally, the behavior of the withdrawn dominant rats may have been altered such that stimuli that maintained the hierarchy and low levels of fighting were no longer (or incorrectly) emitted by this member. Fighting due to loss of stimulus control during withdrawal would be categorized as intraspecific aggression (Moyer, 1968; Eichelman and Thoa, 1973).

Interestingly, identical treatment of the rats led to opposite results in lever-pressing behavior during the withdrawal part of the experiments, depending on the hierarchical position occupied by the subjects. Paired responding by the dominant rats was decreased during withdrawal while this behavior was increased in the submissive members. It is well known that the behavioral effects of drugs are markedly influenced by the rate and temporal pattern of on-going behavior (Dews, 1958; Kelleher, and Morse, 1968). It is possible that withdrawal from drugs that produce physical dependence may have similar rate- and temporal-dependent effects on paired behavior. Moreover, it has been shown that central biochemical changes induced by drugs or stressful conditions are greatly influenced by the types of behaviors the subjects are engaged in at the time treatment is applied (Schoenfeld and Seiden, 1969; Stolk et al., 1974). There may be an interaction between hierarchical position and morphine withdrawal resulting in different biochemical responses between the dominant and submissive rats, which leads to the behavioral differences observed.

Acknowledgements. Supported in part by U.S. Public Health Service Research Grants DA00532 and GM01117.

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Received April 28, 1977; Final Version June 6, 1978