Psychopharmacologia 6, 267—279 (1964)

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Factors Affecting Voluntary Morphine Intake in Self-Maintained Addicted Rats *

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With 1 Figure in the Text

(Received May 14, 1964)

Introduction

Relatively unrestrained rats, prepared with chronically implanted venous cannulas and wearing a saddle connected to a swivel and stuffing box, will maintain an experimental addiction by pressing a lever for morphine (WEEKS 1961, 1962). The number of injections taken varied inversely with the size of the dose, and when the morphine was given on a fixed ratio (FR) reinforcement schedule of 10 (the rat must press the lever 10 times for each injection), the lever responses occurred rapidly and abruptly terminated immediately following the injection. COLLINS and WEEKS (1964) estimated the potency of codeine, dihydromorphinone (Dilaudid) and methadone (Dolophine) relative to morphine in such addicted rats. THOMPSON and SCHUSTER (1964) have demonstrated similar operant conditioning for morphine self-administration using monkeys seated in restraining chairs. DENEAU and YANAGITA (personal communication, WEEKS 1964) have adapted self-administration of morphine to relatively unrestrained monkeys over a period of many months.

WEEKS (1962) noted that changing the dose from 10 to 3.2 mg/kg resulted in about a two-fold increase in the number of doses taken, which was insufficient to sustain the same total daily morphine intake. It was thought that this decreased intake might have resulted from rats adjusting morphine dosage more closely to actual needs. For example, if 6 mg/kg were actually needed, this dose could better be approximated by two 3.2 mg/kg doses than one 10 mg/kg dose. If this explanation were true, a further reduction in the size of the dose should change the total daily morphine intake but slightly.

WEEKS (1962) also noted a decrease in total morphine intake when rats were changed from a continuous reinforcement schedule to a fixed

* A preliminary account of this work was presented at the 25th Meeting of the Committee on Drug Addiction and Narcotics, Natl. Res. Council, Natl. Acad. Sci., Ann Arbor, Michigan, 15—17 February 1963.

ratio schedule of FR-5, but no apparent further decrease at FR-10. Thus, it would be of interest to determine the effect on behavior and total daily morphine intake when the ratio is progressively increased.

Modification of voluntary morphine intake by simultaneous administration of a second drug would be a useful technique in studying drug interactions.

We wish to report, accordingly, the effect of three factors on voluntary morphine intake in addicted rats; 1. progressively decreasing the dose of morphine, 2. progressively increasing a fixed-ratio reinforcement, and 3. continuous administration of a second drug.

Methods

The method of administering drugs[1] was essentially that previously described (WEEKS 1962). The saddle, stuffing box and swivel were of an improved design (for illustration, see WEEKS 1964)[2]. The cannula for intravenous injections was made of silicone rubber, which was far superior to polyethylene originally used (model III, WEEKS and DAVIS 1964). Rats were Wistar origin females, about 250 g at their first morphine injection. Since rats continued to gain weight slowly during the course of an experiment, all drugs were given based upon a 260 g rat. The convenience of the same solution concentration for all rats outweighed any small error. Addiction was established by first administering morphine 2 mg/kg and increasing this dose hourly in a 2.5% geometric progression to 40 mg/kg, the last dose repeated hourly for about one day. At this time the lever was put into the cage, and 10 mg/kg injected for each response. When responses were regular (usually 1 to 3 days), a fixed ratio reinforcement schedule of 5 (FR-5) was started for one day and then rats stabilized at FR-10 for at least two days. Except when a second drug was being given by intravenous infusion, 10 mg/kg doses were given in 0.10 ml volume. During progressive dose reduction, the injection volume was either 0.10 ml or 0.032 ml, and the solutions diluted accordingly.

Intravenous infusion of a second drug. Constant infusions of a second drug were given at 0.64 ml/hr. by a syringe driver[3] through a size

[1] Drugs used were morphine sulfate, codeine phosphate, meperidine hydrochloride (Demerol), nalorphine hydrochloride (Nalline) and etonitazene methanesulfonate [1-(β-diethylaminoethyl)-2-(*p*-ethoxybenzyl)-5-nitrobenzimidazole]. The salts will be understood in all doses.

[2] Catalog No. 1601, Lehigh Valley Electronics Co., Fogelsville, Pennsylvania, U.S.A., or through their distributor Mr. Heinz Albrecht, Box 29, Munich, West Germany.

[3] Model 1100 Infusion-Withdrawal Pump, Harvard Apparatus Co., Dover, Massachusetts, U.S.A.

PE 50 polyethylene "T" tube[1] between the swivel/stuffing box and the injection machine. The voluntary morphine injections were 10 mg/kg in a volume of 0.50 ml. The volume of solution in the cannula and connecting tubing up to the "T" tube was about 0.10 ml, therefore each voluntary injection amounted to only 4/5 of the full dose at once, the the balance being infused during the next ten minutes.

Conditions of the experiments were changed each morning, usually between 0800 and 0900. Since this time was frequently not practicable on week-ends and holidays, the actual duration of each experimental condition varied between 20 and 28 hrs. Accordingly, all results were calculated *pro rata* for a 24-hr. period, which accounts for uneven numbers in the tables.

Results

Progressive dose reduction. Rats were stabilized at 10 mg/kg on a continuous reinforcement schedule for about two days, then the dose reduced about $^1/_3$ each morning in a geometric progression from 10 to 3.2, 1.0, etc. mg/kg. Results for 4 rats are given in Table 1. Down to a

Table 1

Morphine intake by addict rats during progressive reduction of the individual dose

Rat No.		Individual Dose (mg/kg)						
		10	3.2	1.0	0.32	0.10	0.032	0.010
4439	doses/day	22	45	86	190	391	390	
	mg/kg/day	220	144	86	61	39	12	
4384	doses/day	17	38	90	203	172		
	mg/kg/day	170	122	90	65	17		
4519	doses/day	25	64	174	272	363	488	351
	mg/kg/day	250	206	174	87	36	16	4
5066	doses/day	25	70	95	208	335	130	
	mg/kg/day	250	224	95	67	34	4	

dose of 0.32 or 0.1 mg/kg, each time the dose was reduced the total number of doses taken only about doubled. Beyond this point, there was no further increase in number of responses and apparently the amount of morphine being obtained was insignificant. Rats appeared to show a mild abstinence syndrome.

Fixed ratio reinforcement increase. Rats were stabilized at least two days at 10 mg/kg and FR-10. Each morning the FR was increased, first to FR-20 and then in an approximate geometric progression of

[1] Polyethylene tubing Clay-Adams Inc., New York 10, N.Y. Sizes (inside x outside diameters) PE 20 0.38×1.09 mm, PE 50 0.58×0.96 mm. For fabrication of "T" piece, see Section H-2, HEATLEY and WEEKS (1964).

50 percent (20, 32, 50, 75, 120, 180, 270 and 400). FR was increased until the rat obtained less than 4 injections daily. Results for 6 rats are presented in Table 2. Numerical analysis of these experiments proved rather difficult, data is presented in a form intended primarily to describe

Table 2. *Morphine intake, resting time and working time of addict rats following progressive increase in fixed ratio reinforcement*

Rat No.		FR Reinforcement schedule								
		10	20	32	50	75	120	180	270	400
4428	mg/kg/day	120	108	97	80	79	73	71	50	36
	Rest (min)	—*	135	141	167	156	174	172	227	235
	Work (min)	—	3.0	9.6	13	23	24	31	52	167
	% Work	—	2	6	7	13	12	15	19	55
4437	mg/kg/day	200	190	197	115	101	66	55	31	
	Rest (min)	48	48	61	84	117	77	149	223	
	Work (min)	6	10	11	44	26	122	113	239	
	% Work	11	17	15	34	18	39	43	52	
4458	mg/kg/day	145	158	113	95	108	53	54	29	
	Rest (min)	79	74	103	123	124	160	190	242	
	Work (min)	1.2	2.4	4.8	25	60	84	70	256	
	% Work	2	3	4	17	33	34	27	51	
4522	mg/kg/day	154	135	145	152	29				
	Rest (min)	82	82	70	68	115				
	Work (min)	2.4	6.0	6.6	15	377				
	% Work	3	7	9	18	77				
4560	mg/kg/day	169	162	136	121	103	97	78	58	39
	Rest (min)	65	68	95	104	130	130	139	136	156
	Work (min)	2.4	3.6	6.6	9.6	8.4	15	48	115	239
	% Work	4	5	6	8	6	10	24	46	60
4562	mg/kg/day	141	140	121	129	108	94	71	35	
	Rest (min)	102	99	95	96	116	139	155	116	
	Work (min)	1.2	2.4	4.8	5.4	18	20	55	279	
	% Work	1	2	5	5	13	13	26	71	

Morphine dose was always 10 mg/kg.
* Behavior recordings lost.

impressions obtained from examination of records of response patterns and to serve as guides for more critical investigations. The total amount of morphine taken (mg/kg/day) is calculated directly from the number of injections taken and hours on test. Then, each rat's behavior was divided into "working time" and "resting time." Working time was measured from the the start of repeated responses until an injection was received. Resting time, the time from an injection until the rat resumed responses (neglecting sporadic and presumably accidental responses) we considered equivalent to the duration of action of the

morphine injection. In order to allow the rat to become adjusted to each new ratio, calculations were started with the first dose received after a new ratio started and concluded with the last injection received at that ratio. The figures given in the tables are medians. Averages were

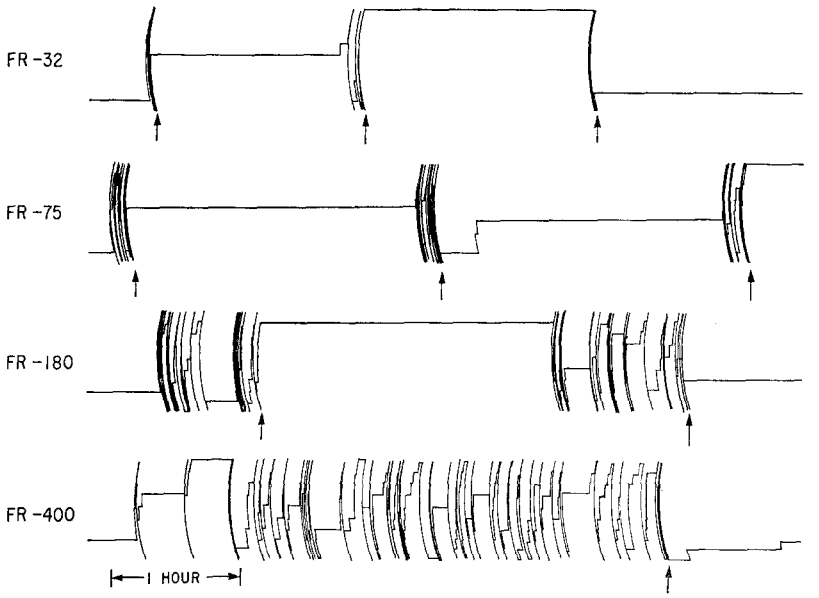

Fig. 1. Representative response records of progressively increasing fixed-ratio performance of addicted rat. Rat received 10 mg/kg of morphine at each arrow. Pen traversed the chart in ten steps, one for each response, and then returned to the base line. Due to mechanical inadequacy, the pen did not always follow trains of very rapid responses, accounting for small discrepancies between counted and recorded responses. Performance is for rat 4560

misleading, since occasionally a rat would take two injections very close together, thus extremely biasing an average resting time. Likewise, when a rat started working for an injection prematurely and then stopped for a while, average working time was biased. Another factor contributing to inaccuracy of these figures is a diurnal variation in morphine intake (COLLINS and WEEKS 1964).

As the "work" required (responses) for each injection increased 12- to 18- fold between FR-10 and FR-120 to 180, morphine intake decreased to about half. Up to about FR-75 responses were generally in single groups, and, once started, continued with only brief interruptions until the injection was obtained. At lower ratios, considering variation and approximation of measurements, working time was roughly proportional to the number of responses required. As the ratios were further increased, rats would stop responding for a few minutes and then resume (Fig. 1). This is illustrated in the disproportionate increase, at the higher ratios,

in percent of the time spent working. At the lower ratios, the resting time (duration of morphine action) changed relatively little while working time may may have increased several fold. However, at the higher ratios there was also a prolongation of the resting time.

Continuous administration of a second drug. Etonitazene is a synthetic opiate-like drug which rats do not find distasteful in their drinking water and which can suppress the abstinence syndrome in morphine dependent animals (WIKLER et al. 1963). This drug was added to drinking water

Table 3
Morphine intake in addict rats with etonitazene (10 μg/ml) in drinking water

Rat No.	Morphine intake (mg/kg) in 6 hr. periods											
	Day 1 Control				Day 2 Experimental				Day 3 Recovery			
	Untreated water				Treated water				Untreated water			
	0800—1400	1400—2000	2000—0200	0200—0800	0800—1400	1400—2000	2000—0200	0200—0800	0800—1400	1400—2000	2000—0200	0200—0800
4560	50	60	90	30	30	0	50	0	50	70	210	150
4583	20	20	30	20	20	0	0	0	10	30	70	50
4581	20	70	50	60	40	20	10	0	20	70	110	110

Rats obtained morphine 10 mg/kg/dose at FR-10 schedule throughout.

(10 mcg/ml) at about 0800 and continued for 24 hrs. After a delay of about 6 hrs., voluntary morphine intake decreased and for the final 6—8 hrs. ceased entirely (Table 3). Upon return to untreated water, morphine intake resumed. The delayed onset presumably was the time required for ingestion of an effective dose of etonitazene. In all rats, during the period 12—24 hours after return to untreated water, morphine intake was at least twice that of the preceding control period. Perhaps the previous etonitazene consumption increased the degree of physical dependence.

Finally, other opiates were administered by intravenous infusion. In addition to morphine itself, codeine, meperidine and the opiate antagonist nalorphine were used. Saline infusions were alternated with drug infusions. No attempt was made to analyze records for any persistence of effect of drug infusion into the control period. Any such effects were not obvious, but may have contributed to increased variation between control periods. The first infusion rate selected was one estimated to have a moderate effect, then increased or decreased to include at least two rates whose effects were between threshold and maximal. (One rat received meperidine infusion at only two rates.) Results for the opiates are summarized in Table 4 and for nalorphine in Table 5.

Table 4. *Voluntary morphine intake by addicted rats during continuous intravenous infusion of an opiate*

Opiate infusion days were alternated with control days during which saline was infused. Control intake is the mean of all controls ± one standard deviation. Voluntary morphine was 10 mg/kg each dose at FR-10

Rat No.	Daily voluntary morphine intake mg/kg								
	Control		Opiate infusion mg/kg/kr.						
		days		1	2	4	8	16	32
			Morphine infusion						
4428	96 ± 12	4	108	72	19				
	% of control		112	75	20				
4439	98 ± 7	4	84	77	29				
	% of control		85	78	29				
4384	106 ± 5	4	101	65	41				
	% of control		95	61	39				
4522	202 ± 17	7	190	221	194	149	120	19	
	% of control		94	110	96	74	60	10	
4519	101 ± 15	5	65	70	60	22			
	% of control		64	69	60	21			
4562	134 ± 33	5	98	60	113*	46			
	% of control		73	45	84	34			
			Codeine infusion						
4439	115 ± 4	3		89	70	60			
	% of control			86	67	58			
4522	266 ± 42	5				180	199	317*	41
	% of control					68	75	119	15
4519	106 ± 14	3			60	41	0		
	% of control				57	39	0		
4562	144 ± 6	4			110	50	19		
	% of control				77	35	13		
			Meperidine infusion						
4428	86 ± 11	5	62	50	34	17			
	% of control		72	58	39	19			
4439	89 ± 15	3	74	29					
	% of control		84	32					
4560	206 ± 37	4		130	67	60			
	% of control			63	33	29			
4581	137 ± 53	4	122	70	34				
	% of control		89	51	25				

* Due to experimental error, rat had no access to morphine the last portion of control period prior to this infusion and was showing mild abstinence signs. This fact may have contributed to excessively high morphine intake.

Table 5. *Voluntary morphine intake by addicted rats during continuous intravenous infusion of nalorphine*

Nalorphine infusion days were alternated with control days during which saline was infused. Control morphine intake is the mean of all controls ± one standard deviation. Voluntary morphine was 10 mg/kg each dose at FR-10

Rat. No.	Daily voluntary morphine intake mg/kg						
	Control		Nalorphine infusion mg/kg/hr				
		days	1/16	1/8	1/4	1/2	1
4407	91 ± 8	4			170	362	293
	% of control				187	397	321
4393	62 ± 5	4			82	125	151
	% of control				131	200	242
4439	106 ± 23	5		161	281	290	257
	% of control			152	266	275	243
4560	139 ± 31	4	187	230	389		
	% of control		134	166	279		
4384	86 ± 16	4		118	320	182	235
	% of control			136	267	211	272
4581	91 ± 18	4		170	247	326	
	% of control			187	271	378	

As expected, infusions of the opiates decreased, while infusion of the antagonist (nalorphine) increased, voluntary morphine intake. Due to the variation among individual rats, quantitative interpretations are again difficult. For morphine infusion, voluntary intake generally decreased as the infusion rate increased. Measurable effects were evident between 0.5 and 1 mg/kg/hr., except for one rat (4522), which had a control voluntary intake about twice that of the other rats. Minimal effects in this high-intake rat were evident between 2 and 4 mg/kg/hr. This greater resistance seemed also to extend to codeine infusions.

Codeine and meperidine infusions were qualitatively similar to morphine infusion. Threshold infusion rates for codeine were obtained in only one rat (4439), since we had expected codeine to be considerably weaker than morphine. All of the codeine infusion rats also received morphine infusion. Comparing only common infusion rates for the two drugs (9 comparisons), in 6 of these codeine infusion was less effective in reducing voluntary morphine intake than morphine infusion. Only two of the rats receiving meperidine infusion also received morphine. Again comparing only common infusion rates (5 comparisons), in 4 meperidine was more effective than morphine.

Effectiveness of nalorphine infusions seems related to the control voluntary morphine intake. Comparing the rat with the lowest control intake (4393, 62 mg/kg/24 hr.) with the highest (4560, 139 mg/kg/24 hr.)

the effectiveness of the nalorphine appeared directly related to control morphine intake. Furthermore, as the rate of nalorphine infusion increased, voluntary morphine intake increased only to a maximum, and more nalorphine did not have additional effect. This relation is definitely so for rats 4384, 4407 and 4439, and in rat 4393 there was only a small further increase at the highest infusion rate. Failure to see this relationship in rats 4581 and 4560 may have been because only lower nalorphine infusion rates were given to these rats.

In all experiments, including infusion of nalorphine, the pattern of responses remained normal, *viz.*, in groups of 10, terminated by the morphine injection. During nalorphine infusion, rats showed signs of an abstinence syndrome (hyperactivity, many soft feces under the cage) in spite of the increased morphine intake. This observation was surprising since we had presumed stopping responses after receiving an injection indicated that nalorphine effects had been overcome.

As with opiate infusions, there was no evidence that the increased morphine intake during nalorphine infusion had any "carry-over" to the control period the following day.

Examination of the effect of morphine infusion upon total intake of morphine (voluntary plus infused) did not show any consistent relationships. With increasing morphine infusion rate, total morphine intake decreased in two rats (4428 and 4439), remained essentially unchanged in three (4383, 4919 and 4562) and increased in one (4522). In the absence of information on blood and tissue levels, interpretation of these results would be pure speculation.

Discussion

Tolerance and physical dependence to the addicting drugs has recently been critically reviewed by SEEVERS and DENEAU (1963). While tolerance and physical dependence usually develop together, these authors point out that they are not the same. Tolerance implies a decreased response to a drug upon repeated administration, and is a widespread occurrence in pharmacology. Physical dependence, in the sense used with addicting drugs, is a latent hyperexcitable state induced by prolonged drug administration, and becomes evident only upon withdrawal of the drug, or, in the case of opiates, the administration of an antagonist. The severity of the *withdrawal illness*, or *abstinence syndrome* would be an indication of the degree of physical dependence. In these experiments there is no true measure of either tolerance or physical dependence and it is not possible to separate the two. NICHOLS et al. (1956) and BEACH (1957) in their work with rats felt that morphine-seeking behavior was based upon drive-reduction (sometimes called escape training) *i.e.*, the

relief of a beginning abstinence syndrome. We believe this same mechanism accounts for self-injection learning, even though overt signs of abstinence were not readily apparent. Assuming that the rats take only enough morphine to relieve abstinence, the total daily intake of morphine would indicate the degree of physical dependence, tolerance being at least sufficient to preclude signs of morphine depression. In humans, ANDREWS and HIMMELSBACH (1944) found that the severity of this abstinence syndrome following abrupt withdrawal was related to the daily dosage of morphine. Similar results have been found for monkeys by SEEVERS and DENEAU (1963, p. 591). The data reported by WEEKS (1962), although not statistically significant, suggested a similar relation for rats. Thus, rats whose tolerance and physical dependence were induced by increasing the morphine dosage to only 20 mg/kg/hr. instead of 40 mg/kg/hr took less morphine (for a 3.2 mg/kg dose, continuous reinforcement, the average daily intakes were 160 and 240 mg/kg/24 hrs, respectively).

Progressive reduction in the dose did not indicate rats would adjust their morphine intake to any fixed requirement, rather the total daily intake decreased as the size of the dose decreased. This result could be interpreted that, with the smaller doses, rats reverted to a lesser degree of physical dependence, much as if the addiction had been induced by smaller doses.

At FR-10, the time taken to obtain the injection was negligible. However, at higher ratios, longer working time in effect imposed a period of abstinence before each morphine injection. SEEVERS (1954) stated that as the abstinence syndrome developed there was a concomitant loss of tolerance to morphine, virtually all tolerance being lost at peak intensity of the abstinence syndrome. In these experiments, the increased resting time (duration of action of the morphine) may indicate decreased tolerance consequent to the period of abstinence. Or, the results could as well be interpreted as decreasing physical dependence due to lower morphine intake. In somewhat the same vein, NICHOLS et al. (1959) suggested that too long a period of morphine abstinence lessened the effectiveness of morphine in drinking water as a reinforcing agent in morphine dependent rats. In any case, our experiments on dose reduction and ratio increase indicate that the size of the dose and its ready availability are factors in maintaining a high voluntary morphine intake.

Continuous administration of opiates and an antagonist had their expected results in a qualitative sense. Codeine infusion was somewhat less effective than morphine infusion, which agrees with the COLLINS and WEEKS (1964) findings that codeine potency was two-thirds morphine by direct substitution in addicted rats. It was surprising that meperidine infusion was at least as effective as morphine, since meperidine by

direct substitution was unable to satisfy physical dependence in sublethal amounts. The infusion permitted meperidine to be given in a sublethal amount, and the balance of physical dependence requirements were met by voluntary morphine. SEEVERS and DENEAU (1963, p. 591) state that many meperidine analogs have such a low convulsant threshold that death occurs before physical dependence can be developed. Nevertheless, because of the limited number of comparisons we hesitate to draw firm conclusions as to the relative potencies of codeine and meperidine compared to morphine.

WIKLER et al. (1953) observed that the effectiveness of nalorphine in inducing withdrawal symptoms in human addicts increased as the daily dose of the opiate (heroin) was increased. This report is in line with the suggested relationship of daily voluntary morphine intake to threshold effect of nalorphine infusions.

Nalorphine is considered to antagonize morphine by occupying receptors responsible for the central depressant effects of morphine (SEEVERS and DENEAU 1963). Given along with morphine it can inhibit the development of tolerance to the analgetic effects of morphine in rats (ORAHOVATS et al. 1953). A similar morphine antagonist, levallorphan, given repeatedly in sufficient doses with morphine, prevented completely the development of physical dependence to the morphine in monkeys (SEEVERS and DENEAU 1962). Apparently the morphine was prevented from occupying its normal receptor sites. SEEVERS (1954) stated that the abstinence syndrome was most intense at the time morphine in the tissues was minimal. If nalorphine infusion displaced almost all the morphine, the abstinence syndrome would then be maximal and the drive for self-injections of morphine also maximal. Further increases in nalorphine infusion rate would not be expected to induce greater morphine intake, and so would explain the "ceiling" effectiveness observed in the rats.

Presence of an abstinence syndrome in spite of increased morphine intake is in line with the report by WIKLER et al. (1953) that additional morphine did not ameliorate the nalorphine induced abstinence syndrome in man.

If the daily voluntary morphine is a measure of the degree of physical dependence as we have postulated, this technique would permit direct evaluation of drugs which have been claimed to modify physical dependence or the abstinence syndrome. For example, using morphine dependent white mice, MAGGIOLO and HUIDOBRO (1962) reported reserpine intensified and iproniazide attenuated the abstinence syndrome induced by nalorphine injection. HUIDOBRO et al. (1963a, b) have also tested a wide variety of drugs and metabolites on this syndrome.

Summary

Self-maintained morphine addicted rats were prepared by implanting chronic venous cannulas and fitting the rats with a device permitting relatively free movement and also enabling them to obtain morphine injections at will by pressing a lever. Three factors modifying voluntary morphine intake were studied. 1. Using a continuous reinforcement schedule, progressively decreasing the size of the morphine dose led to a greater number of doses daily. Compensation was incomplete in that the total daily morphine intake decreased. 2. Progressively increasing a fixed ratio reinforcement schedule up to about FR-75, caused rats to continue responding on the lever until the dose was obtained. Above FR-75 responding became intermittent and daily morphine decreased as the time interval between doses increased. 3. Continuous intravenous infusion of a second drug, leaving voluntary access to morphine at FR-10, led to decreased morphine intake following infusion of morphine itself, codeine and meperidine. Nalorphine infusion increased morphine intake. Effectiveness of infusions varied with the infusion rate.

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