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Comparison of Opioid Agonists in Maintaining Responding and in Suppressing Morphine Withdrawal in Rhesus Monkeys

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Abstract. Sixteen opioid agonists were studied for their capacity both to maintain responding previously reinforced by codeine and to suppress the withdrawal syndrome induced by morphine deprivation in rhesus monkeys. All compounds, which included examples from each of the major chemical families of opioids, maintained responding at rates above those maintained by saline. There were differences among the compounds in the maximal response rates maintained, and large differences in their potencies in maintaining responding. In morphine-dependent monkeys, the abstinence signs that developed 14 h after the last morphine dose were suppressed completely by all of the compounds except codeine. There was a strong positive correlation ($r = 0.92$) between the potency of a compound in maintaining drug-reinforced responding and the potency of the compound in suppressing the morphine withdrawal syndrome.

Key words: Azidomorphine – Codeine – Fentanyl – Heroin – Ketobemidone – Levorphanol – Morphine – Meperidine – Methadone – Propoxyphene – Rhesus monkeys – Drug-reinforced behavior – Drug self-administration – Opioid agonists – Opioid dependence – Morphine withdrawal syndrome

Morphine-like opioids may be identified by their ability to suppress the signs of morphine withdrawal (Seevers and Deneau 1963; Villarreal 1973). Many opioid agonists that suppress morphine abstinence also maintain behavior that leads to their administration. Among the initial demonstrations of this effect were reports by Thompson and Schuster (1964) and Weeks (1962) that morphine-dependent rhesus monkeys and rats would perform discrete operant responses that were followed by IV delivery of morphine. Later workers (e.g. Woods and Schuster 1968) showed that morphine will also reinforce behavior in nondependent subjects. Subsequently, a number of agonists of the morphine-type, including codeine, etonitazene, heroin, *l*-α-acetyl-methadol (LAAM), morphine, methadone, propoxyphene, and etorphine, have been demonstrated to serve as effective reinforcers of drug-taking behavior across a range of routes of administration, access conditions, response requirements, and subject species (e.g. Altshuler et al. 1975; Carroll and Meisch 1978; Carney et al. 1976; Deneau et al. 1969; Downs and Woods 1974; Goldberg et al. 1976; Harrigan and Downs 1978; Hoffmeister 1979b; Hoffmeister et al. 1980; Hoffmeister and Goldberg 1973; Hoffmeister and Schlichting 1972; Hoffmeister and Wuttke 1974; Jones and Prada 1977; Schuster and Balster 1973; Smith et al. 1976; Stretch and Gerber 1977; Wurster et al. 1977; Young and Woods 1980).

The present study describes the self-administration of a number of compounds, from various chemical families, that suppress the signs of morphine withdrawal in the rhesus monkey. The ability of these compounds to maintain behavior was studied under a rapid substitution procedure in rhesus monkeys experienced in self-injecting codeine (Woods 1980). The potencies of the compounds in maintaining drug-reinforced behavior were compared to their potencies in suppressing morphine withdrawal in the monkey.

Materials and Methods

Maintenance of Drug-Reinforced Behavior

Subjects. Male and female rhesus macaques (3–6 kg) were surgically prepared with an indwelling siliconized rubber catheter (Rodhelm Reiss, Belle Mead, NJ; inner diam. 0.08 cm, outer diam. 0.24 cm) under ketamine (10 mg/kg IM) and pentobarbital (15 mg/kg IV) anesthesia. The catheter was placed in a jugular, femoral, or brachial vein, and veins were used successively as needed. The proximal end of the catheter terminated above the right atrium and the distal end passed subcutaneously to a point midway between the scapulae and exited the skin via a stab wound. Additional details of the surgical procedure have been reported by Deneau et al. (1969).

Each monkey was fed approximately 75 g Purina Monkey Chow 45 min prior to each of two daily experimental sessions. Drinking water was available at all times. For the control of tuberculosis, each monkey received a daily sugar cube impregnated with 0.5 ml of an 80 mg/ml isoniazid solution.

Apparatus. Each monkey was housed in an open-faced fiberglass cubicle (Woods 1980) equipped with a stimulus panel containing red and green 7 W stimulus lamps and two response levers (BRS/LVE model PRL-001/121-07, Beltsville, MD). A downward displacement of either lever (10–15 *g* force) was recorded as a response. Each monkey wore a stainless steel harness connected by a swivel to a jointed arm mounted to the back wall of the cubicle (Deneau et al. 1969). The catheter passed from the monkey through the jointed arm to a drug reservoir located behind the cubicle. Solutions were infused through the catheter at a rate of 1.0 ml/5 s by a roller infusion pump (Watson and Marlow, model MHRK 55, Falmouth, England). Programming of the experimental contingencies and data analysis were performed by a PDP 8/I computer (Digital Equipment, Maynard, MA) located in an adjacent room. Cumulative recorders (Ralph Gerbrands, Arlington, MA) and a closed-circuit TV recording system were available to record the behaviors of the subjects.

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Procedure. After postoperative recovery, each monkey was trained to press the right lever when the red stimulus lamp was lit in order to produce a 5-s injection of 0.32 mg/kg codeine. Completion of a fixed ratio (FR) of right lever presses produced an infusion during which the red stimulus lamp was extinguished, a green stimulus lamp was illuminated and lever presses had no scheduled consequences. Each infusion was followed by a time out (TO) period during which both stimulus lamps were extinguished and lever press responses had no programmed consequences. Presses on the left lever had no scheduled consequences at any time. The number of responses required to produce an infusion (the FR value) and the duration of the TO period were increased from FR 1-TO 0 s to FR 30-TO 600 s during successive sessions according to the criteria described by Woods (1980). An experimental session terminated after 130 min or 13 infusions, whichever occurred first. Experimental sessions were conducted twice per day, with at least 4 h between successive daily sessions.

Under these conditions, a codeine dose of 0.32 mg/kg/injection maintains maximal response rates and delivery of all 13 scheduled injections (Woods 1980). The total daily codeine dose (8.32 mg/kg) is lower than the dose necessary to produce physiological dependence in the rhesus monkey (Kolb and DuMez 1931). Stable performance under the FR 30-TO 600 s schedule was characterized by FR response rates over 1.5 responses/s, delivery of all scheduled 0.32 mg/kg codeine injections, few responses on the inactive left lever, and few responses during injections or TO components. When a monkey's performance stabilized, substitution tests were conducted during the afternoon experimental sessions. Saline (0.9% NaCl) was substituted for codeine every fourth experimental session until the saline-maintained response rate fell below 0.2 responses/s or until six saline sessions had occurred. When a monkey displayed low response rates and received few injections during saline substitution sessions, substitution tests were conducted with the various test drugs. Drugs were tested in an unsystematic order, and each monkey received two to six substitution drugs.

Doses of each drug were tested in two separate substitution sessions in each of three monkeys. The initial dose of each drug was approximately one-tenth of the dose necessary to suppress morphine withdrawal in the rhesus monkey (see below). Subsequent doses of each drug were determined by the effects of the initial dose. The injection dose was decreased until a dose was found at which FR response rates and the total number of injections were little higher than those maintained by saline. The injection dose was increased until a dose was reached at which rates were lower than those maintained by the next lower dose. An exception was made to this rule if severe CNS depression or preconvulsive activity was observed by closed-circuit TV monitoring of a monkey during a substitution test. In all such cases, the experimental session was terminated and that dose was not tested further. Drug substitution sessions were separated by at least three sessions of codeine availability. Substitution tests were conducted only when a monkey's codeine-maintained performance revealed no systematic changes in FR response rates or number of injections received over successive codeine baseline sessions. One or more saline substitution sessions were conducted between tests of different drugs for each monkey.

Data Analysis. FR response rate (the rate of right lever presses during the FR components divided by the time, in seconds, elapsed from the onset of the FR components until solution deliveries) and the number of infusions delivered were recorded for each experimental session. The rate of responding on the right lever during infusions and TO periods and the rate of left lever responses over the entire experimental session were also calculated.

Suppression of Morphine Withdrawal Signs

Subjects. A colony of 60–80 male and female rhesus monkeys (2–5 kg) served as subjects in an ongoing drug evaluation program. Each monkey was administered 3 mg/kg morphine SC every 6 h without interruption (7 AM, 1 PM, 7 PM, and 1 AM, respectively) and had received morphine for at least 90 days before drug testing began. The monkeys were housed in groups of four to six in wire mesh pens measuring 1.2 × 1.5 × 2.1 m. The floor of each pen was covered with wood shavings. The monkeys were fed approximately 40–100 g Purina Monkey Chow daily. For prevention of tuberculosis, the chow contained 608.3 g/ton isoniazid. Drinking water was available at all times. The colony room was lighted 7 AM–1 AM daily.

Procedure. The procedures described by Deneau and Seevers (1963) and Villarreal (1973) were used to determine the dose of each drug required to suppress the signs of withdrawal in the 14 h-withdrawn monkey as effectively as 3 mg/kg morphine. In order to quantify the behavioral and physiological signs displayed by the monkeys, the appearance and responsiveness of each subject was graded over time on an eight-grade scale (Deneau 1956; Deneau and Seevers 1963) based on Seevers' (1936) classification of morphine withdrawal signs in rhesus monkeys. Each animal was also graded on a second eight-grade scale for signs of CNS depression (Deneau and Seevers 1963). At each observation period, the withdrawal or depression displayed by each monkey was graded by a trained observer who did not know what drug the subject had received.

Compounds were tested for their ability to suppress completely the signs of morphine withdrawal at a minimum of 1-week intervals. Prior to a drug test, the scheduled 3 mg/kg morphine injections were withheld for 14 h, at which time morphine withdrawal grades of intermediate severity were present. At 14 h withdrawal, the observer injected SC a preselected dose of the test drug, 3 mg/kg morphine, or saline to each of three monkeys. The monkeys' behavior was graded just prior to these injections and at intervals of 0.5 and 1 h after injection. Hourly observation of each monkey continued until its withdrawal score returned to preinjection levels. When observations were complete, the monkeys were administered morphine to terminate withdrawal. The 3 mg/kg dose of morphine suppressed morphine withdrawal signs at 1 h, and withdrawal signs returned to their preinjection severity 5–6 h after 3 mg/kg morphine. If the initial dose of a test drug produced a lesser or greater effect than 3 mg/kg morphine in an individual monkey, the dose was raised or lowered by a factor of 2 during a subsequent test. This testing procedure was repeated until a dose of each test drug was determined that produced graded effects approximately equivalent to those produced by 3 mg/kg morphine in each monkey, or until effects (e. g., convulsions) appeared in such intensity as to preclude further testing. Duplicate observations were obtained in most cases, and different monkeys were usually tested with the different doses of a drug. The doses of each drug that were as effective as 3 mg/kg morphine and the duration of time over which these doses suppressed morphine withdrawal signs were averaged for each of two monkeys. Drugs were tested in an unsystematic order.

Drugs. The following compounds were used: azidomorphine bitartrate; codeine phosphate; fentanyl citrate; heroin HCl; ketobemidone HCl; levorphanol tartrate; meperidine HCl; methadone HCl; morphine sulfate; (+)propoxyphene HCl; UM 747 *[NIH 8439, (–)5-α, 9-α-diethyl-2′-hydroxy-2-methylenecyclopropylmethyl-6,7-benzomorphan HCl]; UM 983 *[NIH 8863, N-(α-pyridyl),N-(1-β-phenylethyl-4-piperidyl) ethylcarbamate HCl]; UM 1076 *[NIH 9112, (±)-3-allyl-1,3-dimethyl-4-phenyl-4-propionoxypiperidine HCl]; UM 1112 *[NIH 9337, (±)-2-cyclopropylmethyl-10-*m*-hydroxyphenyl-*trans*-decahydroisoquinoline]; UM 1113 *[NIH 9338, 2-cyclopropylmethyl-10-*m*-hydroxyphenyl-6-methyl-*trans*-decahydroisoquinoline]; UM 1124 *{NIH 9342; (–)*m*-[2-(cyclopropylmethyl)-1,2,3,4,4a,5,6,7,8,8a-decahydro-4a-isoquinolyl] phenol succinic acid}; and UM 1173 *(NIH 9550, (±)-1-(2-(dimethylamino)ethyl)-6,7-dihydro-3-methyl-4-oxo-6-phenylindole-2-carboxylic acid ethyl ester (E) oxime]. The UM *(NIH) compounds were kindly provided by Dr. A. E. Jacobson of NIH.

All compounds except UM 1112, UM 1113, and UM 1173 were dissolved in saline (0.9% NaCl) or sterile water. UM 1112 and UM 1113 were dissolved in dilute hydrochloride acid, and the pH was adjusted above 5 with $NaCHO_3$. For UM 1173, 8.5% lactic acid was added and the pH was adjusted above 3 with 1.0 N NaOH. For IV administration, solutions were prepared so that all injection doses were delivered in a 1 ml volume. For SC administration, solutions were prepared so that all doses were given in 0.5–1.5 ml volumes. Doses of all drugs except UM 1112, UM 1113, and UM 1173 are expressed as mg/kg salt, and doses of UM 1112, UM 1113, and UM 1173 are expressed as mg/kg base.

Results

Maintenance of Drug-Reinforced Behavior. During the period of substitution tests, the maintenance injection dose of codeine (0.32 mg/kg) maintained average FR response rates of 2.11 responses/s (range 1.26–2.68 responses/s) under the FR 30-TO 600 schedule. All 13 available codeine injections were usually delivered. Substitution of saline for single experimental sessions produced average FR response rates of 0.09 responses/s (range 0.03–0.19 responses/s). Throughout the course of the experiment, very low rates of lever pressing occurred during infusions and TO periods and on the inactive left lever.

Each opioid agonist studied maintained responding at rates above those obtained when saline was substituted for codeine. The FR response rates varied as a function of the compound and its injection dose (Figs. 1–3). In order of potency, the opioids maintained maximal FR response rates at the following injection doses (mg/kg): 0.00003 UM 747; 0.003 azidomorphine, fentanyl, and UM 1076; 0.01 heroin, levorphanol, UM 1112, and UM 1124; 0.03 UM 1113; 0.1 ketobemidone, methadone, and morphine; and 0.3 meperidine. Response rate increased and then decreased as the

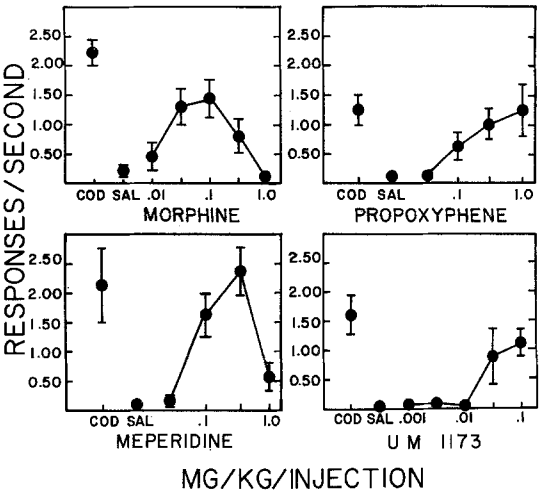

Fig. 2. Response rates during the FR component of the FR 30-TO 600 s schedule of IV drug injection as a function of the injection dose of morphine, propoxyphene, meperidine, and UM 1173 [(±)-1-(2-(dimethylamino)ethyl)-6,7-dihydro-3-methyl-4-oxo-6-phenylindole-2-carboxylic acid ethyl ester (E) oxime]. Details are as in Fig. 1

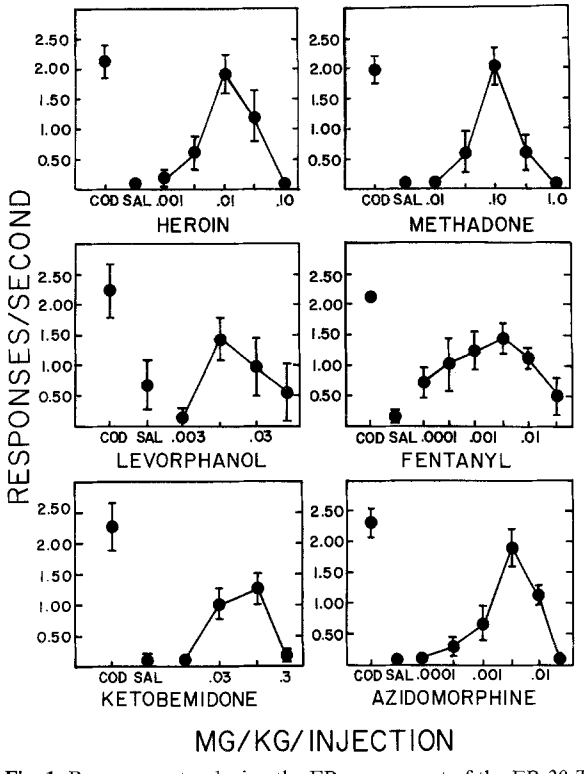

Fig. 1. Response rates during the FR component of the FR 30-TO 600 s schedule of IV drug injection as a function of the injection dose of heroin, methadone, levorphanol, fentanyl, ketobemidone, and azidomorphine: FR response rate in responses/s (ordinates); drug injection dose (mg/kg), log scale (abscissae). Each dose was substituted for 0.32 mg/kg codeine during selected experimental sessions. Each point represents the mean ± SEM of the average FR response rate during two single substitution sessions for each of three monkeys. Points at COD represent the mean ± SEM of the average rate for each subject during two afternoon 0.32 mg/kg codeine-availability sessions during the period of substitution testing, and points at SAL represent the mean ± SEM of the average rate for each monkey during two saline substitution sessions conducted during the period of substitution tests of each agonist

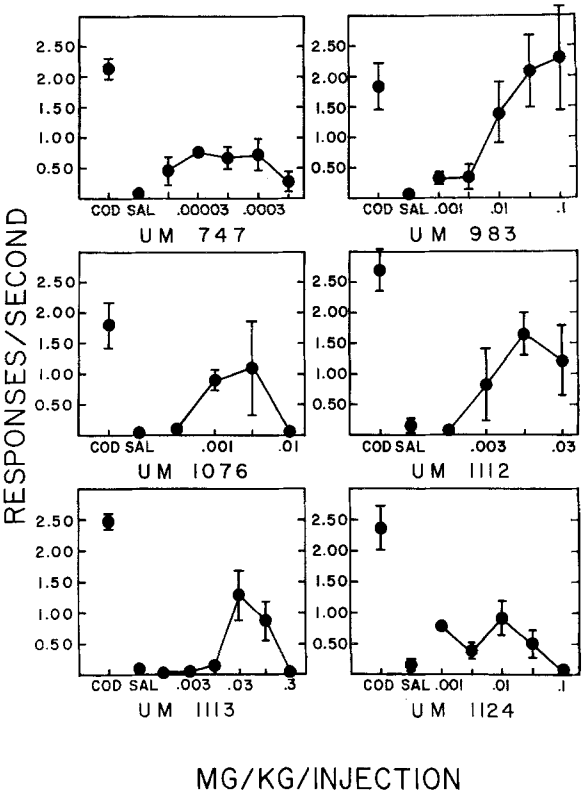

Fig. 3. Response rates during the FR component of the FR 30-TO 600 s schedule of IV drug injection as a function of the injection dose of UM 747 [(–)-5-α, 9-α-diethyl-2′-hydroxy-2-methylenecyclopropylmethyl-6,7-benzomorphan HCl], UM 983 [N-(α-pyridyl), N-(1-beta-phenylethyl-4-piperidyl) ethylcarbamate HCl], UM 1076 [(±)-3-allyl-1,3-dimethyl-4-phenyl-4-propionoxypiperidine HCl], UM 1112 [(±)-2-cyclopropylmethyl-10-*m*-hydroxyphenyl-*trans*-decahydroisoquinoline], UM 1113 [2-cyclopropylmethyl-10-*m*-hydroxyphenyl-6-methyl-*trans*-decahydroisoquinoline], UM 1124 {(–)*m*-[2-(cyclopropylmethyl)-1,2,3,4,4a,5,6,7,8a-decahydro-4a-isoquinolyl] phenol succinic acid}. Details are as in Fig. 1

injection dose increased for all compounds except propoxyphene, UM 983, and UM 1173. Propoxyphene produced preconvulsive activity in one monkey following eight injections of a dose of 3 mg/kg, and this dose was not investigated further. The highest injection doses of UM 983 and UM 1173 tested (0.1 mg/kg) maintained maximal rates. Higher doses were not tested because supplies were depleted.

The potency of an agonist appeared unrelated to the maximal rate of responding maintained by that agonist (Figs. 1–3). FR response rates greater than 2.0 responses/s were maintained by meperidine, methadone, and UM 983. Rates greater than 1.5 responses/s were maintained by azidomorphine, heroin, and UM 1112. FR response rates greater than 1.0 response/s were maintained by all other agonists tested except UM 747 and UM 1124. UM 747 and UM 1124 maintained maximum FR response rates of 0.8 and 0.9 responses/s, respectively.

For most drugs, the dose that maintained maximal response rates maintained performance characteristic of FR schedules throughout the session: When the stimulus light associated with the FR component was illuminated, subjects paused for a time and then pressed the lever at a sustained rate until drug delivery. At doses lower that those that maintained maximal rates, subjects completed several ratios and then paused for prolonged periods. At doses greater than those that maintained maximal FR response rates, subjects rapidly completed several ratios at the beginning of the experimental session, and then responded at lower rates during later FR components. Decreased response rates during the later FR components of the session were also observed at the maximally effective injection doses of morphine, UM 747, UM 1076, and UM 1124.

At the dose of each compound that maintained maximal response rates, subjects received an average of 10 (UM 747 and UM 1076), 12 (fentanyl, ketobemidone, levorphanol, morphine, propoxyphene, UM 1113, UM 1124, and UM 1173) or 13 (azidomorphine, heroin, meperidine, methadone, UM 983, and UM 1112) injections during the experimental session. At higher and lower injection doses, subjects received fewer injections during the 130-min substitution session. For each tested drug, the total dose (mg/kg) injected during the substitution session increased as the injection dose increased.

Suppression of Morphine Withdrawal Signs. All of the compounds studied suppressed the withdrawal signs produced by 14-h withdrawal from morphine. All compounds except codeine suppressed the withdrawal signs completely at some doses. Lower doses decreased the severity of withdrawal, but did not eliminate all signs. Higher doses produced maximum suppression of withdrawal signs and occasionally produced signs indicative of CNS depression.

The doses of the tested compounds that were equivalent to 3 mg/kg morphine in suppressing the signs of withdrawal, and their duration of effect, are presented in Table 1. The potency of the compounds varied over a 1,000-fold range, and the duration of withdrawal suppression varied from a minimum of 2 h to a maximum of 10 h. There was no apparent relation between potency and the duration of suppression of withdrawal signs. Codeine did not completely suppress the withdrawal signs at 20 mg/kg, which produced convulsions. Administration of 15 mg/kg codeine reduced the severity of withdrawal, but did not suppress the signs as completely as did 3 mg/kg morphine.

Table 1. Suppression of the signs of morphine withdrawal in the 14 h-withdrawn rhesus monkey by opioid agonists: Comparison of the doses required for complete suppression and their duration of action

Agonist	Dose (mg/kg) for suppression, in order of potency	Duration of suppression (h)		
		2–4	5–7	8–10
Standard:				
Morphine	3.0		×	
UM 747	0.0125		×	
UM 1076	0.02	×		
Fentanyl	0.04	×		
Azidomorphine	0.20	×		
UM 1112	0.375		×	
Heroin	1.0		×	
Levorphanol	1.0		×	
UM 1113	1.0			×
UM 1124	1.0			×
Methadone	3.0		×	
UM 983	3.0	×		
Ketobemidone	5.0	×		
UM 1173	5.0		×	
Meperidine	10.0		×	
Propoxyphene	16.0		×	

Comparison of the Potency of Tested Compounds in Maintaining Responding and Suppressing Morphine Withdrawal Signs. The potency of the tested opioids in maintaining responding paralleled their potency in suppressing the signs of morphine withdrawal. The dose of each compound which maintained the highest rates of drug-reinforced behavior was plotted against the dose of that compound which was as effective as 3 mg/kg morphine in suppressing morphine withdrawal signs (Fig. 4). There was good agreement between the relative potencies of these compounds in each of the two assays ($r = 0.92$). Compounds which were potent in maintaining responding were also potent in suppressing abstinence (e.g. fentanyl and UM 747). Compounds which required a larger dose to maintain drug-reinforced responding required a proportionately higher dose to suppress morphine withdrawal signs (e.g. meperidine and propoxyphene).

Discussion

The present study demonstrated that a wide variety of opioid agonists that suppressed the signs of morphine withdrawal in the rhesus monkey also functioned as reinforcers of drug-maintained operant behavior in the monkey. Moreover, the relative potencies of the agonists in exerting these two actions showed a high positive correlation.

Compounds from each of the major chemical families of opioids maintained responding leading to their IV injection. Selected examples of morphines (azidomorphine, codeine, heroin, morphine), morphinans (levorphanol), benzomorphans (UM 747), phenylpiperidines (ketobemidone, meperidine, UM 1076) and methadones (methadone and propoxyphene) maintained drug-reinforced behaviors in the rhesus monkey. In addition, representatives of relatively novel chemical classes, including aminopiperidines (fentanyl), phenylindoles (UM 1173), and isoquinolines (UM 1112,

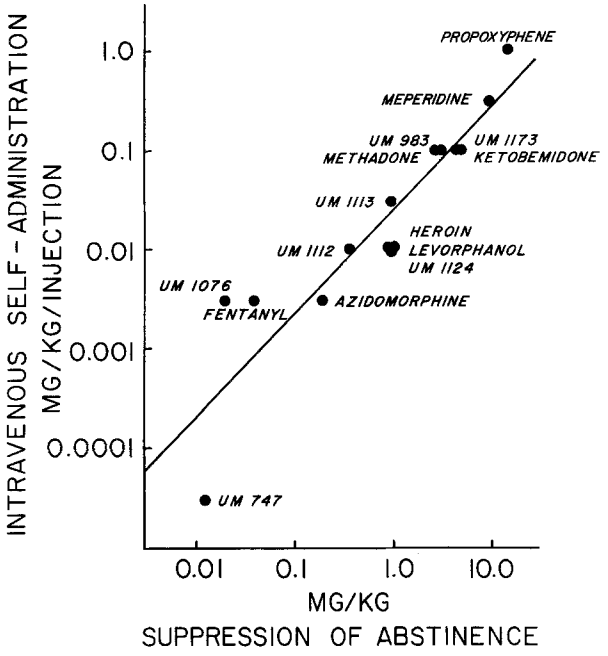

Fig. 4. Comparison of the potencies of morphine-like narcotic agonists in maintaining responding and in suppressing the signs of morphine withdrawal in the rhesus monkey: Injection dose (mg/kg) which maintained maximal FR response rates when substituted for 0.32 mg/kg codeine under a FR 30-TO 600 s schedule of intravenous delivery, log scale (ordinate); drug (mg/kg) SC which suppressed the abstinence signs produced by 14-h withdrawal from 3 mg/kg morphine every 6 h as effectively as 3 mg/kg morphine, log scale (abscissa). The line of best fit was calculated by the least-squares method ($r = 0.92$). The slope of the regression line was 1.04. Structures of the following compounds are as in Figs. 2 and 3: UM 747; UM 983; UM 1076; UM 1112; UM 1113; UM 1124; and UM 1173. See text for other details of the experimental procedure

UM 1113, UM 1124), also maintained drug-reinforced responding. The agonists varied in their potencies as reinforcers and in the actual response rates they maintained. The tested agonists represented a 30,000-fold range of potencies as reinforcers. Certain agonists maintained response rates as high as those maintained by the maintenance dose of codeine, while others maintained maximal rates well below those maintained by codeine. The potency of an agonist as a reinforcer appeared unrelated to the maximum rates of drug-reinforced behavior it maintained.

For each agonist, FR response rate generally increased and then decreased as the injection dose increased within a limited dose range. This relation between injection dose and response rate is the general rule for drug-reinforced behavior under basic schedules of reinforcement (e.g. Goldberg 1976; Pickens et al. 1978). For many drugs, the dose maintaining maximal rates and the actual rates maintained vary as a function of the schedule contingencies and frequency of drug availability (e.g. Goldberg 1973). For a given drug and schedule contingency, certain doses maintain maximal response rates. Lower doses appear less effective as reinforcers under those contingencies, and higher doses are presumed to result in a cumulative effect that slows the rate of responding (e.g. Hoffmeister 1979b). In general, the dose of a drug that maintains maximal rates under a particular schedule, and in turn the doses that are ineffective or cumulative, increases as the interinjection interval increases and the frequency of drug injection decreases. For codeine, for example, doses of 0.01 – 0.05 mg/kg maintain maximal rates under FR 10 or FR 30 schedules, which allow frequent injections (Hoffmeister and Schlichting 1972; Downs and Woods 1974). Increasing the interinjection interval to 10 min under a FR 30-TO 600 s schedule increases the codeine dose that maintains maximal rates to 0.1 – 0.32 mg/kg (Woods 1980; Young and Woods 1980). When codeine availability is further limited to one injection every 3 h, the highest dose tested (16 mg/kg) maintains maximal performance under a progressive ratio schedule (Hoffmeister 1979b). Likewise, for heroin, methadone, morphine, and propoxyphene, the injection dose that maintains the highest rate of behavior under ratio schedules varies directly with the interinjection interval specified by the schedule contingencies (cf. Harrigan and Downs 1978; Hoffmeister 1979a,b; Hoffmeister and Goldberg 1973; Schuster and Balster 1973). The doses of each of these agonists that maintained maximal rates under the FR 30-TO 600 s schedule in the present study were intermediate to those doses that maintain maximal rates under ratio schedules allowing shorter or longer interinjection intervals. Doses of each drug too low to maintain behavior under the FR 30-TO 600 s schedule do maintain behavior under schedules allowing more frequent injections (Harrigan and Downs 1978; Hoffmeister 1979a; Hoffmeister and Goldberg 1973; Schuster and Balster 1973). Doses of codeine, heroin, and propoxyphene too high to maintain behavior under the present schedule maintain ratio responding when available at longer intervals (Hoffmeister 1979b). Thus, for agonists previously studied as IV reinforcers, potencies in maintaining responding in this study were consistent with potencies under related contingencies.

The agonists varied not only in their potencies as IV reinforcers, but also in their apparent efficacies, i. e., in the maximal rates of responding maintained. These differences cannot be readily accounted for by differences in the intrinsic activities of the agonists as opioids, since all were equally efficacious in suppressing morphine abstinence. The compounds are also all equally effective as analgesics in the mouse hot-plate test (Jacobson and May 1965; Tyers 1980; A. Jacobson personal communication). Several factors may have been responsible for the low rates of responding maintained by agonists such as morphine, propoxyphene, UM 747, UM 1076, and UM 1124 in the present study. These compounds may have very slow onset or long duration of action or may act directly to decrease ongoing response rates. Indirect evidence suggesting such action was provided by cumulative records of responding, showing that the doses of these drugs that maintained maximal rates were accompanied by rate decreases during FR components late in the session. In addition, propoxyphene, at 3 mg/kg/injection, produced convulsions following a total dose of 24 mg/kg, precluding further tests of the reinforcing properties of doses that resulted in intakes of this magnitude.

Further studies comparing the onset and duration of action of agonists that maintain different rates of drug-reinforced behavior in the monkey will be necessary to identify the relationship between the speed of onset or duration of effect of a drug and the rates of behavior it maintains. The contribution of any direct rate-decreasing actions of opioid agonists to their maintenance of low response rates under the conditions of this study should be assessed directly by use of longer TO periods to separate

successive injections or by the use of second-order schedules that allow long sequences of behavior to be maintained by relatively infrequent drug injection (cf. Goldberg 1976). The possibility that such direct rate-decreasing actions may be specific to drug-reinforced responding (cf. Woods et al. 1975) should be assessed by the use of multiple schedules of responding maintained by both drug and nondrug stimuli.

Each of the agonists studied, with the exception of codeine, suppressed completely the signs of morphine withdrawal induced by morphine deprivation in the rhesus monkey. The tested agonists did not differ in their efficacy in suppressing abstinence, but differed across a 1,600-fold range in potency and across a five-fold range in the duration of their suppression of withdrawal signs. There was no apparent relation between the potency of a compound to suppress withdrawal signs and the duration of this suppression. The ability of codeine to suppress morphine withdrawal in the monkey appeared to be limited by its convulsant effects (cf. Deneau et al. 1969): A codeine dose slightly below the convulsant dose markedly reduced the severity of, but did not eliminate completely, morphine withdrawal signs.

The potencies of the opioid agonists in suppressing the signs of morphine withdrawal were well correlated with their potencies as reinforcers. Under the experimental conditions used in this study, each compound maintained responding at an IV injection dose roughly one-tenth the SC dose necessary to suppress morphine abstinence in the monkey. The potencies of morphine-like agonists in suppressing withdrawal in the morphine-dependent rhesus monkey also correlate well with their potencies in exerting opioid actions in other systems. Villarreal (1973) reported that the potencies of opioids to suppress morphine withdrawal signs in the monkey generally correlate well with their potencies to suppress morphine abstinence in humans and with their antinociceptive potencies in the mouse. The potencies of opioid agonists in suppressing withdrawal signs in the morphine-dependent monkey also agree with their potencies in exerting opioid actions in vitro. The potencies of morphine-like agonists in suppressing morphine abstinence in the monkey show correlations of over 0.7 with their potencies in suppressing the electrically induced twitch of the guinea pig ileum and of the mouse vas deferens, and with their relative potencies in displacing tritiated etorphine from rat cerebrum membrane preparations (Woods et al. 1981).

Suppression of morphine abstinence can be used to define a compound as a morphine-like agonist in the rhesus monkey (Villarreal 1973). There is good agreement between opioids so defined in the monkey and those which meet Martin's criteria for '*mu*' agonist activity in the spinal dog (cf. Martin et al. 1976). The present results indicate that morphine-like agonists also share the ability to function as positive reinforcers in rhesus monkeys. Further work will be necessary to determine whether the multiple actions of morphine-like opioid agonists are mediated by similar receptor interactions.

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