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Route of administration influences substitution patterns in rats trained to discriminate methadone vs. vehicle

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Abstract

Replacement therapy with the synthetic μ -opioid agonist methadone is an efficacious treatment for opioid abuse. While much is known about methadone's pharmacology, its discriminative stimulus properties remain largely unexplored. The present study sought to establish methadone discrimination in rats. Moreover, some research suggests that route of administration alters the discriminative stimulus of methadone. Thus, the present study also compared intraperitoneal (i.p.) and subcutaneous (s.c.) routes of administration. Male Sprague–Dawley rats were trained to discriminate 3.0 mg/kg methadone (i.p.) from vehicle in a two-lever discrimination procedure. Generalization tests were conducted with a variety of compounds administered i.p. and s.c. Methadone fully substituted for itself, yielding ED₅₀s of 1.5 mg/kg (i.p.) and 0.2 mg/kg (s.c.). Naltrexone (i.p.), an opioid antagonist produced a dose-dependent reduction in methadone-appropriate responding. The methadone stereoisomers fully substituted for methadone when given s.c.; however, when administered i.p., (+) and (–) methadone produced partial and no substitution, respectively. Heroin fully generalized to methadone regardless of administration route, while morphine fully substituted when given s.c., but not i.p. The kappa-agonist U50-488 failed to generalize to methadone with either route of administration. These results demonstrated that methadone's discriminative stimulus is mediated through μ -opioid receptor activity and is similar to that of commonly abused opioids (heroin, morphine). Additionally, route of administration produced differential results for many of the drugs tested, suggesting decreased drug bioavailability following i.p. administration due to hepatic first pass metabolism. Taken together, these results suggest that methadone's shared subjective effects with abused opioids, as well as its unique metabolic properties contribute to its efficacy in opioid maintenance therapy.

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Contributors

Drs. Vann and Porter designed the study. Drs. Vann, Wise, Varvel and Philibin conducted the studies and statistical analyses. All authors contributed to and approved the final manuscript.

Conflict of interest

None declared.

Keywords

Methadone; Heroin; Morphine; Opioid; Drug discrimination; U50-488; Naltrexone; (+) Methadone; (–) Methadone

1. Introduction

Roughly 0.5% of the North American population aged 15–64 meets opioid abuse criteria (United Nations, 2007). Methadone, a synthetic μ -opioid agonist, is an effective treatment option for relieving opioid addiction. Methadone maintenance therapy attenuates withdrawal effects of opioid addiction by providing a stable blood plasma concentration as opposed to the rapid “up-down” fluctuation associated with other opioids (Goldstein, 1972; Inturrisi and Verebely, 1972). This pharmacological property of methadone is key in its therapeutic efficacy. While this pharmacological property is a fundamental characteristic of methadone’s therapeutic efficacy, other pharmacological properties, such as its stimulus properties compared to morphine and heroin, may also contribute to its therapeutic value.

1.1. Discriminative stimulus effects of methadone and other opioids

Preclinically, the stimulus properties of drugs are often evaluated using drug discrimination procedures. In this model, the subjective effects experienced by an animal following administration of a drug serve as internal stimuli that can be discriminated from subjective effects produced by other similar or dissimilar compounds. These subjective effects are believed to mimic the intoxicating effects of that drug in humans (Balster, 1991). Indeed, this model has been valuable in the classification and characterization of the subjective drug effects of many drug classes, such as hallucinogens (Winter, 1994), cannabinoids (Wiley, 1999), antipsychotics (Porter and Prus, 2009) and others. The discriminative stimulus properties of opioids have been investigated extensively in humans and animals (see Dykstra et al., 1997 for review); however methadone has seldom been the primary drug of interest in these studies. Specifically, rats were trained to discriminate methadone in a t-maze drug discrimination (Overton, 1982) and once in a two-lever drug discrimination (Rosecrans and Glennon, 1979). These findings are limited and additional preclinical data regarding the discriminative stimulus properties of methadone would provide a better understanding of its unique therapeutic properties.

1.2. Route of administration alters subjective effects of opioids

While methadone shares many pharmacological properties with abused opioids, its well-established efficacy in the treatment of opioid abuse suggests that methadone might possess a discriminative stimulus different than that of abused opioids. Comparing methadone’s discriminative stimulus properties with those of morphine and heroin may help explain the viability of substituting methadone for morphine or heroin in opioid addicts. Moreover, Rosecrans and Glennon (1979) trained rats to discriminate peripherally administered methadone or morphine from saline and found that morphine centrally administered into the raphe nucleus substituted in both methadone and morphine trained animals. However, centrally administered methadone failed to substitute in either group of rats. The route of administration has been demonstrated to markedly alter the discriminative stimulus properties of methadone and morphine and should be further investigated.

1.3. Purpose of study

The goals of the present study were to establish ($\pm$)-methadone drug discrimination in rats using a two-lever paradigm, assess whether methadone shares discriminative stimulus properties with morphine and heroin, and to determine the mechanism of action of

methadone's discriminative stimulus by testing a μ -opioid antagonist and a κ -opioid agonist. Methadone is given as a racemic mixture comprised of two isomers, (+) and (–) methadone. Since the (–) isomer has been shown to be responsible for the majority of methadone's opioid effects (Scott et al., 1948; Smits and Myers, 1974), (–) methadone might be expected to produce higher levels of substitution for the racemic mixture. Therefore, these stereoisomers were assessed individually to determine if they produced methadone-like responding. Given methadone's unique pharmacokinetic properties, this study evaluated the effects of two routes of administration known to be differentially affected by metabolic processes. The overarching goal of this study was to gain a better understanding of methadone's unique pharmacological characteristics by exploring its discriminative stimulus properties.

2. Methods

2.1. Subjects

Adult male Sprague–Dawley rats (290–340 g) obtained from Harlan Sprague Dawley (Indianapolis, IN) were housed individually in a temperature controlled (22 °C) environment with a 12 h light-dark cycle (lights on at 7 a.m.). After a two-week acclimation period during which the rats had food available *ad libitum*, the weights of the rats were reduced to 85% of their free-feeding body weights. The rats were maintained at this weight with 10–15 g of rodent chow following daily experimental sessions. Water was available *ad libitum* in the home cages. All research conducted in the present study was approved by the Institutional Animal Care and Use Committee at Virginia Commonwealth University and was in accordance with the *Guide for the Care and Use of Laboratory Animals* (Institute of Laboratory Animal Resources, National Academy Press, 1996).

2.2. Apparatus

Rats were trained and tested in standard operant conditioning chambers housed in sound-attenuated cubicles (MED Associates, Georgia, VT). Pellet dispensers delivered 45-mg pellets (P Purified Rodent Diet, P.J. Noyes, Lancaster, N.H.). Fan motors provided ventilation and masking noise for each chamber. House lights were illuminated during training and testing sessions. A computer and MED-PC software (MED Associates) were used to control schedule contingencies and to record data.

2.3. Drugs

(±)-Methadone hydrochloride, naltrexone, and U50-488 obtained from Sigma (St. Louis, MO) and heroin (National Institute on Drug Abuse; Bethesda, MD) were dissolved in VEH (0.9% saline solution). Methadone isomers were kindly synthesized and supplied by Dr. Everett May, Virginia Commonwealth University and were dissolved in VEH. All drugs were administered 30 min prior to training and testing sessions at a volume of 1.0 ml/kg of body weight. For antagonism tests, naltrexone was administered i.p. immediately prior to methadone.

2.4. Procedure

Initial attempts to train rats to discriminate 1.0 mg/kg (±)-methadone i.p. vs. vehicle (VEH) were unsuccessful. Accordingly, the training dose was increased to 3.0 mg/kg methadone. Rats were trained to press one lever following i.p. injection of 3.0 mg/kg methadone and to press the opposite lever after injection with vehicle, each according to a fixed-ratio 30 (FR-30) schedule of food reinforcement. The position of the drug lever was varied among the group of rats. During this procedure, completion of 30 consecutive responses on the injection-appropriate lever resulted in delivery of a food reinforcer and each incorrect response reset the ratio requirement on the correct lever. The daily injections for each rat

were administered in a double alternation sequence of methadone and VEH. Training sessions (15 min) were conducted Monday–Friday until the rats had met three criteria during 8 of 10 consecutive sessions: (1) first completed FR-30 on the correct lever, (2) percentage of correct-lever responding equal to or greater than 80% for the entire session, and (3) response rate equal to or greater than 30 responses/min.

Following successful acquisition of the methadone discrimination, stimulus substitution tests with test compounds were conducted on Tuesdays and Fridays. Training continued on Mondays, Wednesdays, and Thursdays. During test sessions, responses on either lever delivered reinforcement according to an FR-30 schedule. To be tested, rats must have completed the first FR and made at least 80% of all responses on the injection-appropriate lever on the preceding day's training session. In addition, the rat must have met these same criteria during at least one of the training sessions with the alternate training compound (methadone or VEH) earlier in the week.

Initially, a dose effect curve was conducted with i.p. methadone in all rats ($N = 13$). Next, i.p. and s.c. administration of methadone were conducted. Then, the time course effects of methadone's discriminative stimulus were evaluated. For the time course, rats received 3.0 mg/kg methadone (i.p. or s.c.) 15, 30, 60, 120 and 240 min (in ascending order) prior to the test session.

Next, challenge tests were conducted with naltrexone and methadone. First, naltrexone (i.p.) alone was tested. For the antagonist tests, ascending doses of naltrexone were injected (i.p.) immediately prior to i.p. or s.c. 3.0 mg/kg methadone.

Then, rats were divided randomly into two groups ($N = 6-7$) for all subsequent tests. Generalization tests were conducted for i.p. and s.c. administration of morphine, heroin, U50-488, (+) and (–) methadone. Doses of each drug were administered in ascending order. For each drug, rats received each dose for both routes of administration. Throughout the study, control tests with VEH and methadone were conducted prior to the start of each dose–effect curve determination.

2.5. Data analysis

The number of lever presses and the number of reinforcers earned were recorded during each session. Percent drug lever responding (%DLR) was calculated by dividing the number of responses on the drug lever by the total number of responses emitted then multiplying that number by 100. Responses per minute (RPM) were calculated by dividing the total number of responses by the total session length of 15 min. Repeated measures analyses of variance (ANOVA) comparing response rates were performed for the acute and cumulative dose effect curves and for the time course data (GB STAT version 10.0, Dynamic Microsystems Inc., Silver Spring, MD). Significant ANOVAs were followed by Newman–Keuls post hoc tests ($\alpha < 0.05$). ED_{50} s and AD_{50} s (with 95% confidence intervals; CI) were calculated with the least squares method of linear regression on the linear portion of the dose–effect curve for %DLR. To have their %DLR data included in the curve, a rat was required to earn a reinforcer or have completed at least 30 responses during the test session. The following guidelines were used for presenting %DLR data: drug lever responding between 0 and 20% represented no substitution, between 60 and 80% represented partial substitution and 80% or greater represented full substitution.

3. Results

3.1. Methadone

Methadone dose-dependently substituted for itself with an $ED_{50} = 1.2$ mg/kg (CI: 1.0–1.6 mg/kg) (Fig. 1). Repeated measures ANOVA for response rates revealed significant differences in rates of responding as a function of dose ($F(9,108) = 15.4$, $p < 0.05$). Compared with responding following VEH injections, response rates were significantly decreased by 5.6 mg/kg methadone ($p < 0.05$). Comparison data (i.e., from the same rats) for methadone following s.c. and i.p. administration are shown in Fig. 2. As expected, methadone fully and dose-dependently substituted for the 3.0 mg/kg methadone training dose following both routes of administration (upper panel). ED_{50} values for methadone were 1.5 mg/kg (CI: 1–2.1 mg/kg) and 0.2 mg/kg (CI: 0.1–0.3 mg/kg) for i.p. and s.c. administration, respectively. Thus, i.p. administration was between 2 and 8 times less potent than s.c. administration of methadone. Repeated measures ANOVA for response rates revealed significant differences in rates of responding as a function of dose for s.c. ($F(3,15) = 7.0$, $p < 0.05$) but not i.p. ($p > 0.05$) administration (lower panel). Response rates were significantly decreased by 3.0 mg/kg methadone s.c. compared to s.c. VEH control tests ($p < 0.05$).

3.2. Methadone time course

Percent drug lever responding data for the time course effects of 3.0 mg/kg methadone following i.p. and s.c. administrations are shown in Fig. 3 (upper panel). Repeated measures ANOVA revealed significant differences in drug lever responding as a function of time for i.p. ($F[6,36] = 11.8$, $p < 0.05$) and s.c. ($F[6,36] = 9.7$, $p < 0.05$) administration of 3.0 mg/kg methadone. During tests with i.p. administration of 3.0 mg/kg methadone, full generalization was obtained at the 30-min test only. All other tests were significantly different compared to methadone control test ($p < 0.05$). In contrast, s.c. administration of 3.0 mg/kg methadone resulted in near perfect generalization at every time tested except at 240-min.

Repeated measures ANOVA revealed significant differences in rates of responding as a function of dose for i.p. ($F[6,36] = 9.7$, $p < 0.05$) and s.c. ($F[6,36] = 11.4$, $p < 0.05$) administrations of the training dose (lower panel). For i.p. administration tests, response rates obtained during 30 and 60 min tests were significantly decreased compared to SAL test ($p < 0.05$). On the contrary, during s.c. administration tests, all pre-session injection times except for 240-min resulted in significant rate suppression as compared to SAL test ($p < 0.05$).

3.3. Methadone antagonism

Naltrexone dose dependently and completely blocked s.c. and i.p. administration of 3.0 mg/kg methadone (Fig. 4 upper panel). The AD_{50} s for blockade the 3.0 mg/kg methadone training dose by naltrexone were 0.012 mg/kg (CI = 0.005–0.028 mg/kg) and 0.13 mg/kg (CI = 0.07–0.24 mg/kg) for i.p. and s.c. administration of methadone, respectively. Thus, a 10-fold higher dose of naltrexone was required to completely block the substitution of 3.0 mg/kg methadone administered s.c. compared to i.p. Naltrexone (i.p.) failed to substitute for methadone at every dose tested (data not shown).

Responses/min data for both the s.c. and i.p. tests are shown in Fig. 4 (lower panel). Response rates from the naltrexone and i.p. methadone co-administration were not significantly different than i.p. 3.0 mg/kg methadone or SAL alone ($F[4,28] = 1.6$, $p > 0.05$). Repeated measures ANOVA revealed significant differences in rates of responding as a function of dose ($F[3,18] = 7.2$, $p < .05$). For s.c. administration, response rates for all combination naltrexone and s.c. 3.0 mg/kg methadone tests (0.01, 0.1 and 1.0 mg/kg) were

significantly greater than the s.c. 3.0 mg/kg methadone control test ($p < 0.05$). Repeated measures ANOVA conducted on response rate data of naltrexone alone revealed significant differences as a function of dose ($F[5,35] = 3.3$, $p < 0.05$; data not shown). Response rates for all naltrexone doses were not significantly different from SAL control response rates, but were significantly greater than the 3.0 mg/kg methadone control response rates ($p < 0.05$).

3.4. (+) Methadone s.c. and i.p

Percent drug lever responding and response rate data for (+) methadone following i.p. and s.c. administration are shown in Fig. 5 (left panel). (+) Methadone fully and dose-dependently substituted for the methadone training dose following s.c. administration, but failed to substitute when administered i.p. (upper panel). ED_{50} value for s.c. (+) methadone was 0.8 mg/kg (CI = 0.2–2.7 mg/kg). Repeated measures ANOVAs revealed significant differences in rates of responding as a function of dose for s.c. ($F[4,20] = 13.8$, $p < 0.05$) and i.p. ($F[5,25] = 3.3$, $p < 0.05$) (+) methadone administration (lower panel). Compared to corresponding response rates following VEH injections, response rates were significantly decreased by 30.0 mg/kg (+) methadone following both s.c. and i.p. administration ($p < 0.05$).

3.5. (–) Methadone s.c. and i.p

Percent drug lever responding and response rate data for (–) methadone following i.p. and s.c. administration are shown in Fig. 5 (right panel). (–) Methadone fully and dose-dependently substituted for the methadone training dose following s.c. administration, but failed to substitute when administered i.p. (upper panel). ED_{50} value for s.c. (–) methadone was 0.2 mg/kg (CI = 0.1–0.3 mg/kg). Repeated measures ANOVAs revealed significant differences in rates of responding as a function of dose for s.c. ($F[3,15] = 9.6$, $p < 0.05$) and i.p. ($F[4,24] = 7.4$, $p < 0.05$) (–) methadone administration (lower panel). Compared to response rates following VEH injections, response rates were significantly decreased by 1.0 mg/kg (–) methadone administered s.c. and by 10.0 mg/kg (–) methadone administered i.p. ($p < 0.05$).

3.6. Morphine s.c. and i.p

Percent drug lever responding and response rate data for morphine following i.p. and s.c. administration are shown in Fig. 6 (left panel). Morphine fully and dose-dependently substituted for the methadone training dose following s.c. administration, but failed to substitute when administered i.p. ED_{50} value for s.c. (upper panel) morphine was 0.8 mg/kg (CI = 0.2–2.7 mg/kg). Repeated measures ANOVAs revealed significant differences in rates of responding as a function of dose for s.c. ($F[4,20] = 13.8$, $p < 0.05$) and i.p. ($F[5,25] = 3.3$, $p < 0.05$) morphine administration (lower panel). Compared to corresponding response rates following VEH injections, response rates were significantly decreased by 10.0 mg/kg morphine for both s.c. and i.p. administration ($p < 0.05$).

3.7. Heroin s.c. and i.p

Percent drug lever responding and response rate data for heroin following i.p. and s.c. administration are shown in Fig. 6 (center panel). Heroin fully and dose-dependently substituted for the methadone training dose following s.c. and i.p. administration (upper panel). ED_{50} value for s.c. heroin was 0.008 mg/kg (CI = 0.003–0.027 mg/kg), whereas the ED_{50} value for i.p. heroin was 0.444 mg/kg (CI = 0.211–0.933 mg/kg). Repeated measures ANOVA revealed significant differences in rates of responding as a function of dose for s.c. ($F[5,30] = 10.5$, $p < 0.05$) and i.p. ($F[5,30] = 17.1$, $p < 0.05$) heroin administration (lower panel). Response rates were significantly decreased by 0.3 and 1.0 mg/kg heroin s.c. and by 1.0, 1.7 and 3.0 mg/kg heroin i.p. ($p < 0.05$).

3.8. U50-488 s.c. and i.p

Percent drug lever responding and response rate data for U50-488, a κ -opioid agonist, following i.p. and s.c. administration are shown in Fig. 6 (right panel). U50-488 failed to substitute for the 3.0 mg/kg methadone training dose following s.c. and i.p. administration (upper panel). Repeated measures ANOVAs revealed significant differences in rates of responding as a function of dose for s.c. and i.p. administrations. U50-488 administration (lower panel; $F[6,36] = 9.6$, $p < 0.05$, $F[6,36] = 5.2$, $p < 0.05$, respectively). Compared to response rates following VEH injections, response rates were significantly decreased by 10.0 and 20.0 mg/kg U50-488 following s.c. administration ($p < 0.05$) and by 20.0 mg/kg U50-488 following i.p. administration ($p < 0.05$).

4. Discussion

The findings of the present study demonstrate that methadone is capable of serving as a discriminative stimulus in rats and replicates other reports in which methadone was successfully trained as a reference drug (Overton, 1982; Parker et al., 1994; Rosecrans and Glennon, 1979; Schaal et al., 1994). While attempts to train 1.0 mg/kg methadone (i.p.) were unsuccessful, rats readily acquired the 3.0 mg/kg methadone vs. vehicle discrimination. It should be noted that the several of the aforementioned studies used different discrimination procedures (i.e., t-maze, autoshaping) and all used different training doses of methadone, making direct comparisons between the present study and others difficult. This latter point is of particular importance given that training dose is a crucial component of a drug's discriminative stimulus properties, as demonstrated by this study. Other drug discrimination studies have also demonstrated this principle with the opioids morphine (Young et al., 1992) and fentanyl (Zhang et al., 2000) as well as other drugs (e.g., Porter et al., 2000; Stolerman et al., 1984; White and Appel, 1982). When administered s.c., methadone was 2–8 times more potent than when administered i.p. Thus, route of administration greatly influences the potency of methadone.

4.1. Naltrexone blocks methadone's discriminative stimulus and rate suppressant effects

A pharmacological challenge with the opioid antagonist produced full and dose-dependent blockade of methadone-appropriate responding, regardless of methadone's route of administration in the present study. While naltrexone also has activity at non-opioid receptors (e.g., dopamine receptors in the nucleus accumbens; Di Chiara and Imperato, 1988; Spealman and Bergman, 1992), blockade of methadone's discriminative stimulus by naltrexone demonstrates μ -opioid receptor activity mediation. Naltrexone also has been shown to block the discriminative stimulus effects of other opioids, such as heroin and morphine in many species, including rats, monkeys and pigeons (for review, see Krimmer and Barry, 1982). In the present study, naltrexone successfully reversed the rate suppressant effects of methadone demonstrating that these effects also are mediated through the μ -opioid receptor. It should be noted that naltrexone is active at all three opioid receptors. However, naltrexone has greatest affinity for μ -opioid receptors in Sprague-Dawley rats (Giordano et al., 1990). Further evidence for the μ -opioid pharmacological specificity of the methadone discriminative stimulus was provided by failure of the μ -opioid agonist U50-488 to substitute for methadone regardless of route of administration.

4.2. Route of administration alters substitution patterns of morphine

In the present study heroin fully substituted for methadone following both i.p. and s.c. injections, whereas morphine only generalized when administered s.c. These findings highlight methadone's ability to serve as a suitable replacement for morphine and heroin in dependent patients, as it is subjectively similar to these abused drugs. Previously, methadone has been shown to substitute for heroin (Cook and Beardsley, 2004; Newman et al., 2002)

and generalize to morphine administered s.c. (Holtzman, 1982; Overton, 1982; Young et al., 1992) and i.p. (Gianutsos and Lal, 1975). In the present study, i.p. administrations of morphine failed to produce meaningful methadone-like responding, even at doses that significantly disrupted response rates. This result strongly suggests that rate suppression is not a salient component of methadone's discriminative stimulus. However, the distribution of %DLR data for the 10.0 mg/kg dose was mixed, with two out of the six rats tested fully substituting for methadone (91.8 and 100% DLR). One rat failed to respond at this dose, while the other three responded with 0, 0, and 34.9% DLR. Given that drugs of the same pharmacological class tend to cross-generalize for one another (Balster, 1990), the failure of i.p. morphine to fully substitute for methadone is somewhat surprising.

4.3. Route of administration alters substitution patterns of methadone isomers

The substitution pattern observed with morphine (i.e., full substitution following s.c. injection; no substitution following i.p. injection) also was observed with methadone's two stereoisomers, (+) and (–) methadone. The substitution differences observed may be attributed to routes of administration potency differences, with s.c. administration being more potent. One possible explanation for these potency differences is the first pass hepatic metabolism associated with i.p., but not s.c. injections. It is important to note that methadone is typically given in an oral racemic formulation which, like i.p. administration, also undergoes first pass metabolism when ingested. Indeed, most compounds tested required higher doses to substitute for methadone and/or induced rate suppression when given i.p., suggesting a substantial decrease in methadone bioavailability following first pass metabolism. Thus, i.p. administration of methadone may more accurately model the metabolism of orally consumed methadone. There were also noticeable potency differences not attributable to route of administration between the two stereoisomers, with (–) methadone being 100 times more potent than (+) methadone.

It has long been suggested that the (–) isomer of methadone is responsible for its opioid effects (Scott et al., 1948; Smits and Myers, 1974), thus it was not surprising that it substituted for methadone. However, a growing body of literature indicates that (+) methadone exerts its effects via NMDA receptor antagonism (Inturrisi, 2005), making its substitution for methadone somewhat surprising. The substitution of (+) methadone for the racemic mixture in this study has several possible explanations. NMDA antagonism might be a salient component of methadone's discriminative stimulus. Attempting to antagonize both isomers with naltrexone and additional generalization testing with other NMDA antagonists would help substantiate or refute this. Conversely, (+) methadone's substitution may also be the byproduct of nonspecific effects, given the sharp increase in methadone-appropriate responding between 10.0 and 30.0 mg/kg (+) methadone. Indeed, altering the ratio of the two isomers in the racemate is of interest in an effort to enhance methadone's therapeutic efficacy on an individual basis (see Eap et al., 2000).

4.4. Route of administration alters methadone time course

Route of administration differentially affected the time course of methadone's discriminative stimulus. Methadone administered s.c. produced full methadone responding 15 min after injection, lasting until 120 min, whereas i.p. methadone only produced full substitution during the training time (30 min). This finding is interesting given the long half-life of methadone relative to other opioids (Trescot et al., 2008), but is consistent with another study. Specifically, in heroin trained rats, a decline in heroin-appropriate responding was demonstrated 2 h after s.c. administration of 3.0 mg/kg methadone (Newman et al., 2002). Moreover, this difference in onset and duration of methadone's discriminative stimulus may explain why some compounds (i.e., morphine, (+) and (–) methadone) only substituted for methadone when administered s.c.

4.5. Conclusions

In conclusion, the present findings suggest that methadone's therapeutic properties are due to its shared subjective effects with heroin and morphine and its unique metabolic characteristics relative to other opioids. Route of administration was shown to produce disparate substitution patterns in several of the drugs tested (i.e., methadone isomers, morphine). Moreover, route of administration influenced the potency of nearly all the drugs tested, as s.c. injections required lower doses to produce maximal drug lever responding and to suppress responding compared to i.p. injections. These differences are likely due to pharmacokinetic differences associated with the two routes of administration. Overall, the discriminative stimulus and metabolic properties of methadone described in this study contribute to a better understanding of the unique therapeutic characteristics of methadone.

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Fig. 1.

Effects of methadone on percentage of methadone-lever responding and response rates following i.p. administration in rats trained to discriminate 3.0 mg/kg methadone from vehicle ($N=13$). Points above VEH and METH represent the results of control tests with vehicle and 3 mg/kg methadone conducted before each dose-effect determination. Values represent the mean ($\pm$ SEM). Asterisks (*) indicate a significant decrease ($p < 0.05$) in response rates compared to mean rates of responding occurring during the VEH tests.

Fig. 2.

Effects of methadone on percentage of methadone-lever responding (upper panel) and response rates (lower panel) following s.c. or i.p. administration ($N=6$). Points above VIP, MIP, and VSC represent the results of control tests with i.p. administration of vehicle and 3.0 mg/kg methadone and s.c. administration of vehicle, respectively. All other details are the same as Fig. 1.

Fig. 3. Time course effects of i.p. and s.c. administration of 3 mg/kg methadone ($N = 7$) on percentage of methadone-lever responding (upper panel) and response rates (lower panel). All other details are the same as Fig. 1.

Fig. 4.

Methadone challenge with i.p. administration of naltrexone on percentage of methadone-lever responding (top panel) and response rates (bottom panel) following s.c. or i.p. administration of 3.0 mg/kg ($N=7$). All other details are the same as Fig. 1.

Fig. 5. Effects of (+) methadone (left-hand panels) and (-) methadone (right-hand panels) on percentage of methadone-lever responding (top panels) and response rates (bottom panels) following s.c. or i.p. administration ($N=6-7$). All other details are the same as Fig. 1.

Fig. 6. Effects of morphine (left-hand panels), heroin (center panels), and U50-488 (right-hand panels) on percentage of methadone-lever responding (top panels) and response rates (bottom panels) following s.c. or i.p. administration ($N = 6-7$). All other details are the same as Fig. 1.