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Gender differences in the intravenous self-administration of mu opiate agonists

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Abstract

Gender differences have been observed in a number of aspects of the pharmacology of opiates, including their antinociceptive activity, discriminative stimulus properties, the generation of physical dependence, and their positive reinforcing properties. The current experiments were carried out to rigorously examine whether gender differences exist in the intravenous (IV) self-administration of opiates in an operant conditioning paradigm. Both dose–response analyses and the determination of the strength of the reinforcing properties of opiates using a "breakpoint" analysis were examined. We found strong gender differences in the IV self-administration of two mu opiate agonists—heroin and morphine. At a standard fixed ratio (FR) of responding, females consumed significantly greater amounts of heroin and morphine than did males in a dose-dependent fashion. In addition, females also showed much higher breakpoints than did males: the highest FR breakpoint achieved in females was more than double that observed in males and the frequency distribution of breakpoints was shifted significantly to the right in females when compared to males. These data collectively show that mu opiate agonists may serve as reinforcing agents in females over a broader dose range than males and that they also self-administer considerably more opiates on a milligram per kilogram basis. Finally, we conclude that they will also expend much greater effort in an operant conditioning task to obtain opiate reinforcement.

Keywords: Self-administration; Gender differences in self-administration; Opiates, gender differences; Heroin, self-administration; Morphine, self-administration; Heroin, gender differences; Morphine, gender differences

Gender differences have been observed in a number of the aspects of the pharmacology of opiates, including the antinociceptive activity of morphine and other mu agonists in the rat (Boyer et al., 1998; Cicero et al., 1996, 1997; Cook et al., 2000; Krzanowska and Bodnar, 1999), their discriminative stimulus properties (Craft et al., 1996, 1998), the generation of physical dependence (Cicero et al., 2002a; Craft et al., 1999), and their positive reinforcing properties (Alexander et al., 1978; Cicero et al., 2000; Klein et al., 1997; Lynch and Carroll, 1999). Recently, it has been shown that the gender differences observed in morphine-induced analgesia in the rat are mediated primarily by the organizational effects of steroids, which occur in the developing rat brain, as opposed to their acute activational effects in adulthood (Cicero et al., 2002b).

These gender-related differences raise the important issue of whether there may be gender differences in the abuse liability of opiates. Surprisingly, there is a paucity of preclinical and clinical literature in which potential differences in the abuse potential of opiates have been assessed. The absence of relatively little systematic data related to this important point is somewhat surprising, since it has been reported (Clemmey et al., 1997; Dudish and Hatsukami, 1996; Griffin et al., 1989; Kandel et al., 1997; Kosten et al., 1995; Lex, 1991; Rapp et al., 1995) that male and female human substance abusers may differ in the severity of their abuse, may have different treatment outcomes, and/or require different prevention strategies.

Despite the absence of a systematic database, a few studies have been reported in the preclinical literature in which the reinforcing or rewarding properties of heroin or morphine were examined. For example, in a recently published study from this laboratory (Cicero et al., 2000), we

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found that morphine generated a place preference for the drug chamber in both males and females, but there were marked differences in the dose–response curves. Morphine induced a strong place preference over a much broader dose range in females than males. While these data suggest that there may be differences in the reinforcing properties of morphine, they are indirect and do not directly assess the rewarding aspects of the opiates. Only self-administration studies can assess this issue and, perhaps, have more direct relevance to abuse liability issues.

A relatively small number of studies have examined the self-administration of opiates (morphine or heroin) using both oral (Alexander et al., 1978; Hadaway et al., 1979; Hill, 1978; Klein et al., 1997) and intravenous (IV) self-administration (Lynch and Carroll, 1999; Stewart et al., 1996). Using the most well-validated paradigm—IV self-administration—Lynch and Carroll (1999) found that females acquired self-administration of opiates at a much faster rate than males; although there was a trend for females to administer more heroin than males in these studies, this difference was not significant. In contrast to these studies, Stewart et al. (1996) failed to find any gender differences in the IV self-administration of heroin. Given the apparent inconsistencies in these two studies, the current experiments were carried out to rigorously examine whether gender differences exist in the IV self-administration of opiates over a broader range of behavioral and pharmacological conditions. Both dose–response analyses and the determination of the strength of the reinforcing properties of opiates using a "breakpoint" analysis were examined.

1. Methods

1.1. Humane care of laboratory animals

All of the experiments and protocols employed in these studies were reviewed and approved by the Institutional Animal Care and Use Committee.

1.2. Materials

Sprague–Dawley male and female rats, 60 days of age, were purchased from Harlan Sprague Dawley (Indianapolis, IN). Self-administration catheter sets were purchased from Med-Associates (Lafayette, IN). Heroin and morphine-sulfate were generously provided by the National Institute on Drug Abuse (Bethesda, MD).

1.3. IV self-administration

Male and female rats, which were food restricted to 85% of their initial body weight, were first trained to press a lever to obtain food pellets in an operant conditioning chamber (Med-Associates) The rats were well trained for a period ranging from 4 to 8 weeks at an FR8 ratio. The rats were then allowed to feed ad libitum for 3–5 days before surgery to recover their body weight loss. For the surgical procedures, rats were anesthetized using 1 ml/kg of an anesthetic cocktail (100 mg/ml ketamine HCl, 20 mg/ml xylazine HCl and 10 mg/ml acepromazine) and were then surgically implanted with indwelling IV catheters by procedures described elsewhere (Hemby et al., 1996). The rat's catheters were maintained clot-free by the infusion of 200 μl heparinized saline every 99 min, 24 h a day, 7 days per week, in their home cages. Five days following the surgery, the rats were placed in the IV infusion chambers (Med-Associates). They were infused with 200 μl heroin (15 μg/infusion) as a priming dose prior to the initial daily session to initiate self-administration behavior; in subsequent test sessions, no priming dose was used. Each daily test session lasted for 4 h. The rats were initially placed on an FR1 schedule of reinforcement. Once stable levels of responding were achieved for at least 4 days (< 10% variation), the FR increased to FR4. A period of 4 days of stable responding was used as the criterion to ensure that the task was completely acquired and to control for possible differences in the estrous cycle in females. Only rats which met a criterion of at least 10 infusions/4-h test session were used in the experiments described in the results. Body weights were recorded weekly. The patency of the catheters was also assessed weekly by the infusion of 10 mg/kg brevital. If no response occurred immediately (head droop or loss of consciousness) the rats were excluded from the experiment.

1.4. Dose–response analysis

Once stable levels of responding for 15 μg/infusion of heroin were achieved at an FR4 ratio (4 days at >10 infusions per 4-h session), the dose of heroin was changed to assess dose–response characteristics. The doses used were 1.25, 3.75, 15.0, 22.5, and 30 μg/200 μl infusion. The doses were tested under a computer-generated random sequence for each animal. Doses were adjusted only when stable levels of responding occurred (< 10% variation) for 4 consecutive days. A total of 24 males and females were utilized in these experiments.

1.5. Breakpoint analysis

In a separate group of animals, the breakpoint was determined by procedures described elsewhere (Roberts et al., 1989). In these studies, morphine, rather than heroin, was used as the reinforcing agent to make these results directly comparable to the extensive series of studies in which gender differences have been observed in the pharmacological profile of morphine. The breakpoint was defined as the maximum FR within each 4-h session at which point responding for morphine ceased. Rats (48 males and females) were initially trained to infuse heroin at 15 μg/infusion at a FR4 ratio. Once stable levels of responding occurred, the animals were then shifted to morphine infusions (150 μg/200 μl infusion). When stable

levels of responding were achieved for four consecutive sessions, the rats were placed on a progressive ratio (PR) schedule of responding in which the response rate was doubled after each infusion within each 4-h session. Rats began at FR4, and then, after each infusion, the FR was doubled (FR8, 16, 32, and so forth) until the animals failed to respond any further. The breakpoint was defined as the last FR which maintained responding. Rats were used in the procedures for as long as the catheters remained patent (minimum of 2 to a maximum of 10 weeks). The highest breakpoint achieved during this entire period was used as the unit for analysis in these experiments.

2. Effects of opiates on operant rates of responding for food reinforcement

To ascertain whether opiates stimulated or suppressed operant behavior in general, as opposed to a specific effect on self-administration rates, 12 female and 12 male rats were trained to self-administer food pellets using an FR1 schedule of reinforcement; 20 reinforcements were possible during each 40-min daily session. Once the behavior was acquired (>85% correct responses), the rats were shifted to a variable interval (VI) schedule of reinforcement (VI—120 s). In this paradigm, a light above the active lever remained on for the session's entirety, but the active lever delivered a food pellet only after the appropriate interval had passed. The rats had to respond within 10 s of the VI elapsed time. Once the active lever was pressed, the VI would randomly change, causing the lever to be inactive until the new VI time span had elapsed. This cycle was repeated throughout the 40-min sessions each day. During this time, the number of times the correct and incorrect levers were pressed and the number of reinforcements given to the rats were recorded. From this data, the percentage of correct lever presses was calculated and recorded. When the behavior was fully acquired (>85% correct responses) with stable levels of responding (±10% variation in total response rates) for 5 consecutive days, each rat was then subjected to injections of saline and various morphine concentrations (0.5–10 mg/kg), subcutaneously. Morphine and saline were administered 15 min prior to each operant session. Each rat was given saline (1 ml/kg) for 2 days, and then the test dose of morphine for 2 days, and returned again to saline for 2 days. This cycle was repeated until stable levels of responding (±10%) at greater than 90% correct responses were achieved for 4 consecutive days at the test dose of morphine. Morphine doses were tested in the following order (computer-generated random sequence): 2, 5, 3.5, 1, 3, 7.5, 0.5, and 10 mg/kg.

2.1. Statistical analysis

All statistically significant differences were assessed by a two-factor ANOVA ($P<.05$) in the dose–response experi-

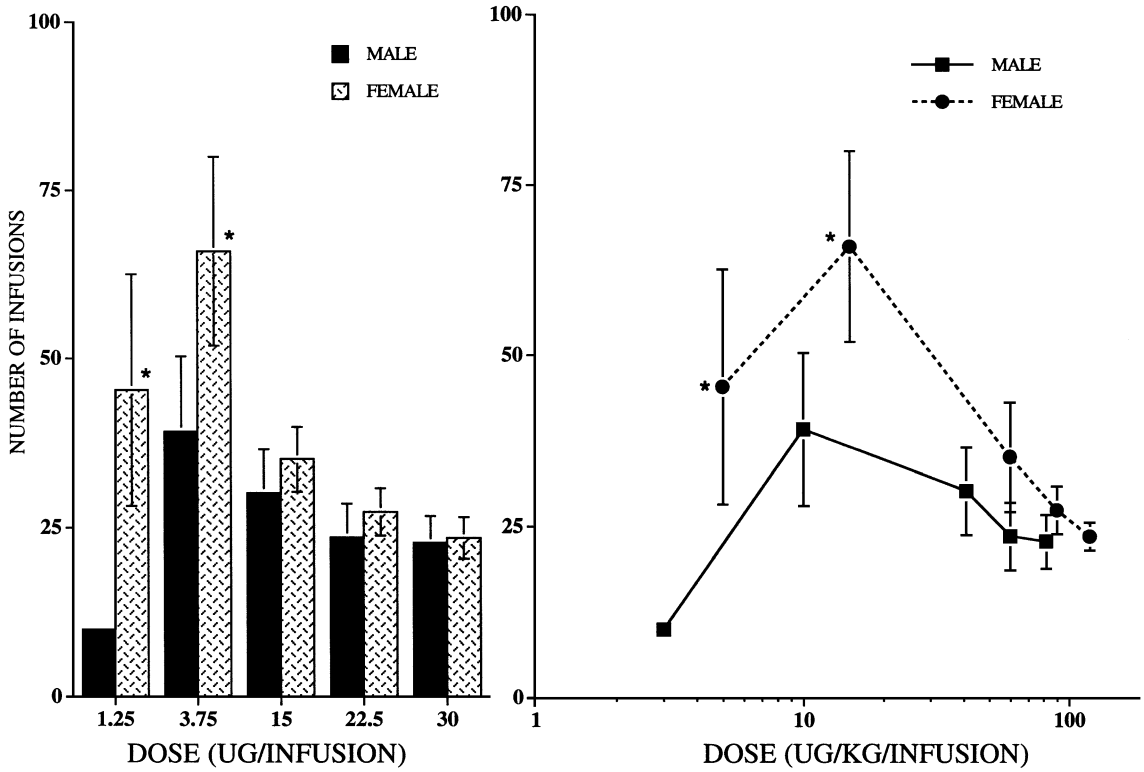

Fig. 1. Mean (±S.E.M.) number of infusions of heroin self-administered by males and females ($N=24$ in each group) as a function of the dose of heroin, expressed as μg/infusion in panel A, or as mg/kg/infusion in panel B, to correct for differences in body weight. * Significantly ($P<.001$) higher than in males.

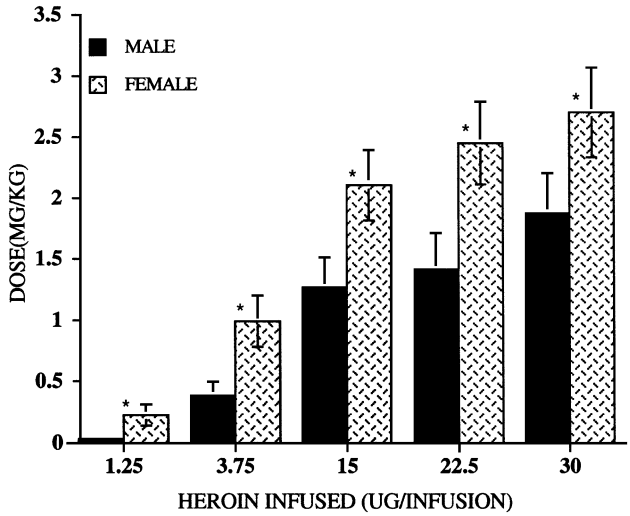

Fig. 2. Mean (±S.E.M.) dose of heroin self-administered (mg/kg) in male and female rats ($N=24$ in each group) at the heroin concentrations (200 μl) infused in the self-administration paradigm. Significant ($P<.001$) differences were observed between males and females at each concentration of heroin.

ments; Newman–Keuls post hoc tests were used to assess specific significant effects. A *t* test was used in the breakpoint analysis using the computer program PRISM (Graph Pad, San Diego, CA).

3. Results

3.1. Dose–response analysis

Fig. 1A and B shows the number of infusions taken in the heroin dose–response analysis. The data are presented as number of infusion versus dose of heroin, expressed as micrograms heroin/200 μl infusion (panel A, which was the standard infusion volume for both males and females), and numbers of infusions versus heroin dose expressed as micrograms/kilogram/infusion to adjust for the large gender differences in body weight (panel B). As can be seen, the number of infusions taken by females was higher than for males at each dose of heroin, but this difference was significant ($P<.001$) only at the two lowest doses tested. As the dose increased, females continued to infuse marginally more heroin, but none of these differences was significant. It should be noted that a much larger number of females (8 of 24) infused the lowest dose of heroin than did males, only one of which responded for the lowest dose of heroin (1 of 24). In terms of the total amount of heroin self-infused per daily session, however, it is apparent females took much larger absolute amounts of heroin, on a milligram/kilogram basis, than did males (Fig. 2) due to their much lighter body weights, at all heroin infusion concentrations. This difference was particularly striking at the lowest concentrations of heroin used, at which females took more than twice as much heroin as males. At the higher dose ranges, females

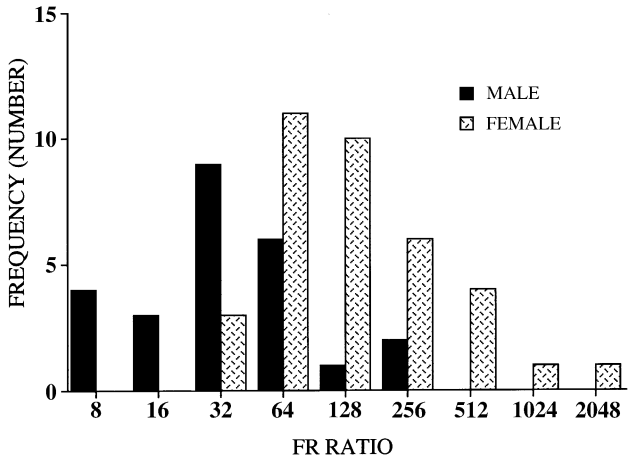

Fig. 3. Frequency distribution of the total number of males and females responding at the break-points shown on the *x*-axis. The break-point was defined as the highest FR ratio at which the animals failed to respond for morphine self-infusions.

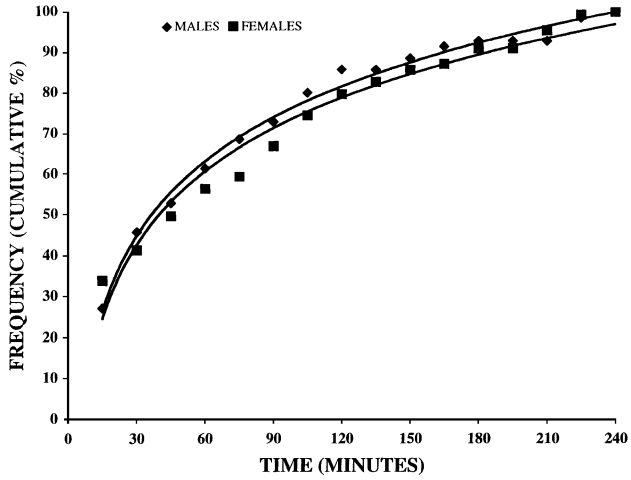

Fig. 4. Cumulative frequency, as percent of control, for males and females as a function of time during the 4-h test sessions.

took significantly more heroin, but the magnitude of these differences was somewhat smaller than that observed at lower doses.

3.2. Breakpoint analysis

Fig. 3 shows the frequency distribution of the breakpoints which occurred in males and females. Although there was some overlap, the frequency distribution in females was shifted markedly to the right (i.e., higher breakpoints) when compared to males. The frequency distribution also shows that a significant number of females achieved breakpoints exceeding FR512 compared to none in males. In terms of mean differences, females showed breakpoints that were more than twice that observed in males (FR of 220.63 ± 58.39 vs. 98.33 ± 28.002, respectively).

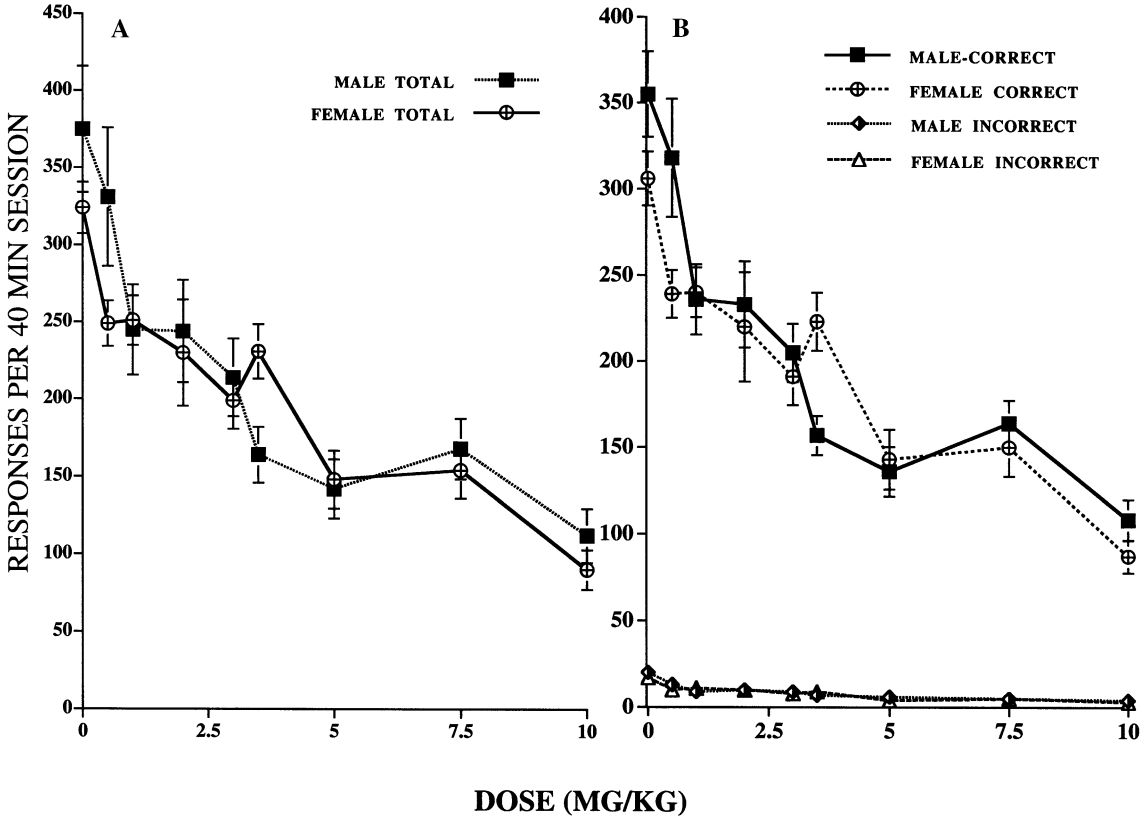

Fig. 5. Effects of morphine (mg/kg) on total response rates for food reinforcement in males and females (Panel A) and the number of correct and incorrect responses (Panel B). Values are mean (± S.E.M.) of 10 animals per group.

3.3. Acquisition of self-administration and the estrous cycle

A substantially higher number of females acquired the self-administration task (4 days of stable responding at greater than 10 infusions/4-h test session) than did males in all animals used in the dose–response and breakpoint analysis: 53 of 72 females acquired the task compared to only 37 of 72 males. We observed no differences in females in response rates over the 4-day criterion period of stable responding, suggesting that there were no differences in the self-administration of heroin or morphine engendered by the estrous cycle.

3.4. Pattern of responding

Fig. 4 shows the cumulative number of morphine infusions occurring in each 4-h test session in the breakpoint analyses for females and males (expressed as a percent of total). As expected from the data shown in Fig. 3, males self-administered significantly fewer infusions of morphine over the 4-h infusion period than did females as a result of the lower breakpoints achieved. In terms of the pattern of the distribution of infusions over time, however, there were no gender differences (Fig. 4). That is, the best-fit lines (Fig. 4), which are best described by logarithmic curves in both sexes, clearly overlapped. For the first 2 h of the infusion session, the rate of responding in both males and females increased in a near-linear fashion as indicated by the slope of the best-fit line; from 2 to 4 h, the slope decreased significantly, indicating that the rate of increase was markedly slower in both sexes. Nevertheless, the pattern of responding was identical in both sexes, suggesting that the primary gender difference was in the amount and number of infusions rather than in their relative distribution over time.

3.5. Influence of morphine on self-administration rates for food pellets

Fig. 5A and B shows the effects of morphine (mg/kg) on total responses (panel A)—both correct and incorrect responses—for food pellets and total correct and incorrect responses (panel B). There were no differences between male and female rats in terms of the suppressant effects of morphine on operant responses—either as a function of total response rate or percent correct responses which averaged greater than 95% correct in both sexes.

4. Discussion

The results of these studies indicate that strong gender differences exist in the IV self-administration of two mu opiate agonists—heroin and morphine. At a standard fixed ratio (FR), females consumed significantly greater amounts of heroin and morphine than did males in a dose-dependent fashion. In addition, females also showed much higher breakpoints for morphine self-administration than did males. These results appear to reflect differences in the potency or efficacy of heroin and morphine as reinforcers, as opposed to any nonspecific change in behavior. We found no gender differences at doses comparable to those achieved in this self-administration paradigm, in the effects of morphine on rates of responding for food pellets which indicates that the likelihood that morphine nonspecifically suppressed behavior (i.e., rates of responding for both food reinforcements and self-administration of opiates) seems improbable. This possibility needed to be examined carefully to ensure that the rates of responding for the self-administration of heroin or morphine, particularly in the breakpoint analyses, was specific to self-administration of heroin or morphine and not a more general effect of behavioral suppression. These data as a whole indicate that females self-administer more opiates, both in terms of the absolute amount of opiate self-infused and the amount of work that will be expended to obtain reinforcements in an operant conditioning paradigm. It is not possible at this time to ascertain whether morphine is more efficacious or potent in females than in males. Further experiments are required to address this point. Nevertheless, it is clear that under the conditions employed in these studies, there were significant differences in the self-administration of heroin and morphine in the rat.

The present results are consistent with the limited number of self-administration studies carried out to date. For example, in agreement with Lynch and Carroll (1999), we found that more females than males acquired the IV self-administration task. These authors also found that females tended to self-administer more heroin than males, but this difference was not significant, whereas we found very robust gender differences, particularly in terms of the dose of heroin (μg/kg) self-administered, and the breakpoint analysis. Neither of the latter were examined in the study by Lynch and Carroll (1999). Similarly, our results are in agreement with earlier morphine oral ingestion studies in which females tended to take more morphine than males under a variety of circumstances (Alexander et al., 1978; Hadaway et al., 1979; Hill, 1978; Klein et al., 1997). Thus, although we recognize the limitations and questions of pharmacological relevance with oral self-administration paradigms, these earlier experiments would generally tend to confirm the present results and those of Lynch and Carroll (1999).

Our results, however, disagree sharply with those published by Stewart et al. (1996). These investigators found no gender differences in the IV self-administration of heroin. We have no explanation for the differences in our results, but there are several factors which could be involved. For example, we found a very large, significant increase in the number of heroin infusions taken by females when compared to males at very low doses of heroin, but only marginal differences at higher doses such as those used by Stewart et al. (1996). It seems possible that Stewart et al. (1996) may have failed to observe gender differences

because of dose–response issues. Moreover, we found that there were substantial differences in the actual dose of heroin (μg/kg) taken and in the breakpoint analysis, neither of which were examined by Stewart et al. (1996). Finally, it should be noted that we used very large *N* in our studies and, given the overlap in frequency distributions observed in breakpoints between males and females, it may not be unreasonable to suggest that studies utilizing fewer animals may have failed to detect the large differences we have observed in the IV self-administration of heroin and morphine.

An important aspect of the present studies is our observation that at very low doses of heroin, many more females than males self-administered the drug. One reasonable interpretation of these findings is that females were able to discriminate heroin at lower doses than males. Some support for this conclusion has been provided by Craft et al. (1996, 1998). These investigators found that females detected morphine at much lower doses in a drug discrimination paradigm than males. Based upon the findings, it may not be unreasonable to suggest that the present results may indicate simply that females self-administered heroin at much lower dose levels than males because of their enhanced ability to detect the drug. On the other hand, it seems equally plausible to suggest that there were no differences in detection, but that females found lower doses of heroin reinforcing, whereas males did not. Our results do not permit a resolution between these two plausible explanations. Additional studies should be carried out to examine more fully the apparent gender differences in the detectability of opiates, possible differences in their reinforcing properties and the mechanisms which might be involved.

The present results are in agreement with results published by Roberts et al. (1989) with an entirely different substance of abuse—cocaine. These investigators found, utilizing the same breakpoint analysis we employed in the current studies, that females would work much harder than males to obtain cocaine in an IV self-administration paradigm. While not directly comparable, the present results and those of Roberts et al. (1989) suggest that female rats may find several drug classes—stimulants and opiates—more reinforcing than do males. The validity of these conclusions should be examined in additional studies.

Whether gender differences might exist in drug-taking behavior and abuse liability in humans remains to be determined, but the present results are predictive that such differences might be found. While there remains a paucity of clinical literature in which potential differences in the abuse potential of all drugs, but particularly opiates, have been assessed, a number of recent studies (Clemmey et al., 1997; Dudish and Hatsukami, 1996; Griffin et al., 1989; Kandel et al., 1997; Kosten et al., 1995; Lex, 1991; Rapp et al., 1995) indicate that male and female substance abusers may differ in the severity of their abuse. The results reported in this paper, together with previous preclinical studies (Alexander et al., 1978; Hadaway et al., 1979; Klein et al., 1997; Lynch and Carroll, 1999), suggest that direct studies of gender differences in drug-seeking behavior in humans should be of very high priority.

The scope of sex-related differences in all aspects of opiate pharmacology appears to be substantial. A large number of studies have shown significant differences in opiate antinociception with male rats being much more sensitive to morphine than females (Boyer et al., 1998; Cicero et al., 1996, 1997; Cook et al., 2000; Krzanowska and Bodnar, 1999). Craft et al. (1996, 1998), reported that morphine served as a discriminative stimulus at lower doses in females than in males. In addition, it has been shown that the expression of physical dependence is greater in males than females (Cicero et al., 2002a; Craft et al., 1999). Given that it has been shown that there may be differences in the rewarding properties of opiates in the present studies and earlier ones (Cicero et al., 2000; Klein et al., 1997; Lynch and Carroll, 1999), it appears that there is a complex pattern of gender differences in the pharmacology of the opiates: in some aspects of opiate pharmacology, females appear to be more sensitive to morphine's effects (e.g., its discriminative stimulus properties), in others, markedly less sensitive (e.g., antinociception), and in the present studies, that they self-administer much larger amounts of mu agonists than males. The mechanisms underlying these robust gender differences in the pharmacology of the opiates are largely unknown, and these broad, fundamental differences need to be more fully explored.

In prior studies, there was some speculation that the gender differences observed in opiate antinociception could be due to more rapid metabolism of morphine in female rats resulting in somewhat lower effective brain concentrations. While some studies have suggested that this may be at least part of the explanation (Candido et al., 1992), other experiments (Cicero et al., 1996, 1997; Nock et al., 1998) have shown no effects, and the overall differences reported, if any, have been rather small. Since the gender differences observed in opiate pharmacology are complex, with females more or less sensitive than males, a biodispositional explanation seems insufficient. In addition, the IV self-administration of opiates leads to a rapid uptake into the brain with metabolic differences playing little role in the overall effects. Thus, it seems highly unlikely that the prior gender differences observed in the pharmacology of the opiates and the results reported here are an artifact related to biodispositional factors; rather, the evidence seems clear that there are fundamental differences in the sensitivity of the nervous system to morphine.

The nature of the differences in neuronal sensitivity to morphine is unknown. However, if one makes the logical assumption that sex-related differences in the pharmacology of the opiates observed in the present and earlier studies are in some manner due to differences in the central nervous system sensitivity to morphine, one reasonable hypothesis is that there are differences between males and females in the number or affinity of those opiate receptors involved in

mediating these effects. In this connection, Hammer (1984, 1985) has reported sex-linked differences in the number and regional distribution of opioid receptors in sexually dimorphic brain regions in males and females. In addition, there is some evidence to suggest that steroids may modulate opiate receptor populations in a number of areas of the brain (Brown et al., 1996; Eckersell et al., 1998; Hammer et al., 1994; Quinones-Jenab et al., 1997; Wagner et al., 1998). Finally, we have observed (Cicero et al., 2002b) that the organizational effects of sex steroids on the development of gender-specific brain regions may account for nearly all of the gender differences observed in opiate-induced antinociception. Given that differences have been found in the reinforcing properties of the opiates in the present studies, which are mediated by multiple, specific sites in the nervous system, future research should be directed toward establishing a convergence between steroid-sensitive neural systems, gender differences in opiate receptors in sexually dimorphic brain regions, and those areas thought to be involved in the rewarding aspects of the opiates. In this manner, the brain regions, and ultimately the mechanisms which may be involved in the gender differences observed in the reinforcing properties of the opiates, might be more thoroughly evaluated.

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