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Gender Differences in the Reinforcing Properties of Morphine

THEODORE J. CICERO, TERRI ENNIS, JUSTIN OGDEN[1] AND EDWARD R. MEYER

Washington University School of Medicine, Department of Psychiatry, 4940 Childrens Place, St. Louis, MO 63110

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CICERO, T. J., T. ENNIS, J. OGDEN AND E. R. MEYER. *Gender differences in the reinforcing properties of morphine*. PHARMACOL BIOCHEM BEHAV **65**(1) 91–96, 2000.—The purpose of the present studies was to examine whether gender differences could be observed in an important aspect of morphine's pharmacology: its reinforcing properties. Our results showed that morphine served as a positive reinforcing agent in both male and female rats in a place conditioning paradigm, but that the dose–response curves displayed marked sex-related differences. At doses from 0.2 up to 10.0 mg/kg, morphine induced an equally strong preference for the drug-associated chamber in males and females. However, as the dose was increased from 10–17.5 mg/kg, morphine ceased to act as a positive reinforcer in males. In contrast, a very strong preference for the morphine-associated chamber was still observed in females at doses up to 30 mg/kg. No gender differences in the blood and brain levels of morphine were observed subsequent to morphine administration during the conditioning phase, suggesting that pharmacokinetic factors were not involved in the sex-related differences observed. Consequently, these results suggest that there are intrinsic sex-linked differences in the doses of morphine that can induce a preference for the drug-associated chamber in a place-conditioning paradigm that are most likely related to differences in the sensitivity of the central nervous system to morphine's reinforcing properties in males and females. © 1999 Elsevier Science Inc.

Gender differences Opiates, reinforcing properties Morphine, reinforcing properties Opiates, gender differences Morphine, gender differences

WE (11,12) and others (2,5,22,24) have previously shown that male rats are more sensitive to morphine's antinociceptive effects than females. Craft et al. (13,14) have also observed that morphine served as a discriminative stimulus at lower doses in females than in males, providing further evidence of sex-linked differences in the acute response to morphine. These sex-differences in morphine's acute pharmacological profile do not seem to be related to pharmacokinetic or bioavaiblity issues, because small (13) or no gender difference (11,12,14) have been found in morphine blood and brain levels at the doses and times used to assess antinociception or morphine's discriminative stimulus properties.

The purpose of the present studies was to address the possibility that gender-related differences might be observed in the reinforcing properties of morphine—a key component of its abuse liability. We are unaware of a single study in humans examining gender differences in the abuse liability of opiates, which is surprising because it has been suggested that there may be sex differences in the abuse of cocaine and alcohol, and perhaps in drug abuse treatment strategies and outcome measures (3,17,25–28).

In the preclinical literature, there is a similar paucity of data. In fact, we are aware of only one study that has directly addressed the issue of gender differences in the reinforcing properties of opiates. Stewart et al. (31) found no differences in heroin self-administration patterns between male and female rats; there were no dose-related differences in the amount of heroin self-administered or in the maximal fixed-ratio schedule at which self-administration ceased (i.e., the "break-point"). Interestingly, Roberts et al. (29) observed significant gender differences in the break points for cocaine self-administration in rats with females reaching much higher FR ratios than males. In addition, a number of investigators have documented sex-related differences, albeit somewhat variable in the direction of differences, in the self-administration of alcohol (16,23). Given the relatively few studies in

Requests for reprints should be addressed to Theodore J. Cicero, Ph.D., Washington University School of Medicine, Department of Psychiatry, 4940 Childrens Place, St. Louis, MO 63110. T. J. Cicero is a recipient of a Research Scientist Development Award DA00095.

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which sex-related differences in the reinforcing properties of psychoactive drugs have been examined, it is clearly premature to conclude that sex differences exist in the reinforcing properties of cocaine and alcohol, but not for opiates, as the current literature might suggest. More definitive studies are needed before any such conclusion would be warranted.

In an effort to provide additional evidence related to this important aspect of the abuse liability of opiates, we have examined whether there are sex differences in morphine's reinforcing properties in a place-conditioning paradigm. Place conditioning procedures have been used rather extensively in the substance abuse field to characterize the positive reinforcing properties of drugs with significant abuse liability (4,10, 27,30). Consequently, we used this procedure to examine whether gender differences could be demonstrated in the dose–response characteristics of morphine's positive reinforcing properties. To ensure that any gender-related differences observed in the morphine dose–response curve were due to sex-related differences in the sensitivity to morphine, as opposed to pharmacokinetic variables, blood and brain levels of the drug were measured during the conditioning phase to ensure that they were equivalent at comparable doses in males and females.

METHODS

Materials

Sprague–Dawley derived rats were purchased from Harlan–Sprague–Dawley, Indianapolis, IN. They were used at 70–90 days of age at the start of all studies described in this article. Morphine-sulfate was purchased from Sigma Chemical Co., St. Louis, MO. The place preference apparatus was custom made to our specifications by MedAssociates (Lafayette, IN), and is described in more detail below. The iodinated morphine radioimmunoassay kit was purchased from Diagnostic Products Corporation (Los Angeles, CA). The antibody is specific to morphine with less than .03% crossreactivity for morphine-3-glucuronide and less than 0.1% crossreactivity for morphine-6-glucuronide. The lower limit of sensitivity of the assay was 125 pg, and the standard curve was linear over the range 125 to 2,500 pg ($r = 0.97$). Interassay variation was 3% and intraassay variation was less than 5% in all studies described in the article.

Place-Conditioning Apparatus

The place-conditioning apparatus consisted of three compartments with photobeams spaced at 5 cm, which enabled computerized recording of time spent in each of the chambers. The choice chamber ($4.75 \times 8.25''$) consisted of gray Plexiglas walls and floors and was positioned between two equally sized test chambers ($8.25 \times 11''$). Computerized guillotine doors separated the choice chamber from the two test chambers, which were constructed to provide uniquely different environments for the conditioning phase of these studies. One chamber was made of smooth white Plexiglas walls with wire-mesh flooring, whereas the other chamber consisted of textured black Plexiglas walls with the floor consisting of metal bars (0.15 inch in diameter) spaced at 0.5 inch.

Place-Conditioning Procedure

During the acclimation phase, rats were not injected with drugs, but rather were simply placed in the choice chamber for 5 min, after which the guillotine doors automatically opened giving them access to either the white or black chamber for a 15-min period. The amount of time spent in each chamber was recorded. This phase continued for 5 days and established the baseline (i.e., drug-free) preference for either the black or white chambers for all statistical analyses. Day 5 was used to define the baseline. After this baseline period, the conditioning phase began. Groups of male and female rats ($n = 6$ in each group) where injected subcutaneously with saline or morphine, and were then immediately placed in the morphine- or saline-associated chamber for 60 min with the doors closed to prohibit any movement out of the chamber. The doses of morphine used were as follows: for males, 0.2, 0.5, 1.0, 1.5, 2.0, 2.5, 5.0, 7.5, 10.0, 12.5, 15.0, and 17.5 mg/kg; for females, the same doses were used as in the males except doses of 20, 25, and 30 mg/kg were added as the upper range of the dose–response curve.

Because initial testing under baseline, drug-free conditions showed that both male and female rats displayed a preference for the black chamber, morphine injections were paired with the nonpreferred white chamber and saline with the preferred black chamber. However, in eight groups of animals, morphine was given in the preferred chamber and saline in the nonpreferred chamber as a means of validating that this procedure was measuring morphine's reinforcing properties, as opposed to some other action of the drug [for a discussion of place preference paradigms and possible confounding variables see (10)]. The conditioning phase continued for 12 days with animals receiving one injection per day of either saline or a single dose of morphine on each day; the order of injections was randomly determined by a computer program. Animals were injected 5 days per week.

On the test day, the animals were not injected but were placed in the gray choice chamber for 5 min, after which the doors automatically opened. The animals were then allowed to choose between the white or black chamber for a 15-min period, and the total time spent in each chamber was recorded to determine whether a preference developed for the morphine-associated chamber (see Analysis of Data section for the definition of preference). This procedure was repeated multiple times with different groups of animals until complete dose–response curves of morphine's positive reinforcing properties could be established. To determine whether a preference for either the white or black chamber developed over the course of the conditioning phase that was unrelated to drug administration, 10 groups of males and females were given saline in both the white and black chambers and then tested as described above.

Serum and Brain Levels of Morphine

Morphine serum and brain levels were measured in separate groups of adult male and female rats injected with doses of morphine ranging from 1.5 to 30 mg/kg. The doses were selected to span the range of doses over which maximal sex-linked differences were observed in morphine's positive reinforcing properties in the place conditioning procedure. Groups of 10–15 animals were sacrificed by decapitation after the morphine injections at representative intervals used in the 60-min conditioning phase (i.e., 15, 30, or 60 min); serum and whole brain were collected. Serum levels of morphine were determined in unextracted samples by the radioimmunoassay kit described above. Whole brains were homogenized in 0.1 N NaOH and allowed to dissolve overnight at 0–4°C. Morphine brain levels were measured directly in those extracts by RIA. Protein levels were measured by the method of Bradford (6), and concentrations in brain were expressed as ng morphine/mg protein.

Analysis of the Data

A "preference score" for the morphine-associated chamber was defined by subtracting the time spent in the saline-associated chamber from the time spent in the morphine-associated chamber according to the following formula: (time in morphine-associated chamber during test − time spent in saline-associated chamber during test) − (time in morphine-associated chamber during baseline − time in saline-associated chamber during baseline) = total shift in time spent in morphine-associated chamber as a result of the conditioning phase (preference score in seconds).

Using this formula, if the animals displayed no shift in preference for either the saline- or morphine-associated chamber as a result of the conditioning phase, the preference score would be zero. On the other hand, a positive preference score indicated a shift in preference for the morphine-associated chamber induced by morphine relative to base-line (i.e., drug-free), whereas a negative integer score indicated a preference for the saline-associated chamber (i.e., no preference was established for morphine-associated chamber).

All differences between males and females were analyzed by a multifactor analysis of variance (sex × dose) to determine whether a preference for the morphine-associated chamber was generated, compared to saline, and whether differences existed between the dose–response curves of males and females. In this analysis, only doses from 0 (saline) to 17.5 mg/kg were included because there were no matching data in males for the doses of 20, 25, and 30 mg/kg used in females. Newman–Keuls post hoc tests ($p < 0.05$) were used to evaluate differences between all sets of means.

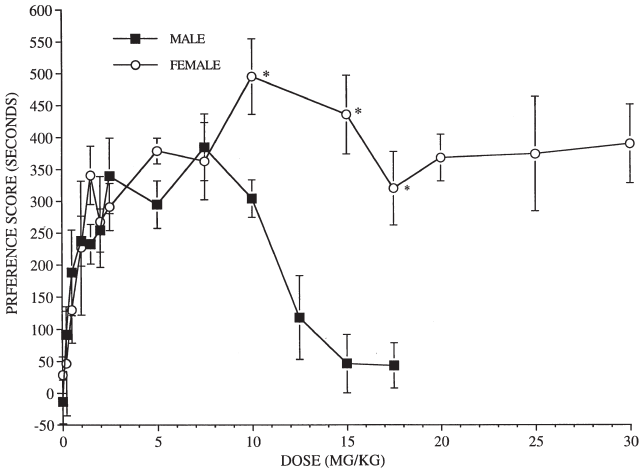

FIG. 1. Dose-response curves for morphine's positive reinforcing properties in male and female rats; values are means (±SEM) of two to three replicate experiments ($n = 6$ in each experiment) at each dose. The preference score was determined according to the formula described in the Method section. In control groups (i.e., saline given in both chambers), the "preference score" was −45.02 (±25.3) and 23.7 (±18.3) s in males and females, respectively. There was statistically no significant sex-related differences in either baseline preference scores or those observed in controls (i.e., saline rather than morphine injections) during the conditioning phase. In this figure at morphine doses in excess of 0.5 mg/kg a significant shift occurred in the preference score when compared to control (saline) values at all doses in both males and females. *Significantly ($p < 0.01$) greater than males.

RESULTS

General Considerations Regarding the Place-Conditioning Paradigm

During the acclimation phase both male and female rats displayed a preference for the black chamber, with females showing a significantly greater preference than males (time spent in white − time spent in black): −122.1 (±19.6) s vs. −26.35 (±15.81) s, respectively. On the basis of these findings, morphine injections were generally paired with the nonpreferred white chamber, and saline with the preferred black chamber. However, in eight groups of males and females, the morphine-associated chamber was reversed (i.e., morphine injections were associated with the preferred, black chamber) to validate that the preference for the drug-associated chamber was not an artifact of the particular chamber selected for conditioning (8). A preference for the morphine-associated chamber of approximately the same magnitude was observed no matter which chamber had been associated with the opiate and, hence, all of the results described in this article represent the pooled results of morphine given in either the black or white chamber. When saline was given in both the black and white chambers during the conditioning phase (see Fig. 1), the preference score was essentially zero (i.e., no preference developed for either chamber).

Morphine Dose–Response Curves in Males and Females

Figure 1 shows the dose–response analysis of morphine's positive reinforcing effects in male and female rats. Analysis of variance revealed a significant sex difference, $F(1, 408) = 11.84$, $p < 0.001$, and a significant interaction of sex × dose, ($F(11, 408) = 3.65$, $p < 0.001$). Newman–Keuls analysis of all pairs of means yielded the levels of significance ($p < 0.05$) discussed below and those shown in the figures.

An inverted U-shaped dose–response curve was found in male rats. At doses from 0.2 to 2.5 mg/kg, the preference score for the morphine-associated chamber increased in a near linear fashion. This substantial preference for the morphine-associated chamber remained essentially constant over the dose range of 2.5 to 10.0 mg/kg (Fig. 1). At doses above 10 mg/kg, there was a sharp drop in the preference score, such that at the highest doses used (12.5–17.5 mg/kg) there was only a slight, nonsignificant preferences for the drug-associated chamber when compared to controls. Although morphine was also found to act as a positive reinforcer in females, the shape of the dose–response curve was not an inverted U, as was true for males. The preference score for the morphine-associated chamber increased exponentially from 0.2 to 7.5–10.0 mg/kg, as was the case in males, but there was no significant decline in the preference score as the dose was increased to 30 mg/kg. An upper limit for the dose of morphine at which it no longer served as a positive reinforcer in females could not be determined, because doses over 30 mg/kg were toxic resulting in a high lethality rate (>30%).

Blood and Brain Levels of Morphine

Figure 2 shows the blood and brain levels, respectively, attained 60 min after the injection of morphine at the doses used during the conditioning phase in the place-conditioning paradigms. Doses lower than 1.5 mg/kg produced blood and brain levels that were not detectable by the radioimmunoassay for morphine. There were no differences observed between males and females in the peak blood or brain morphine

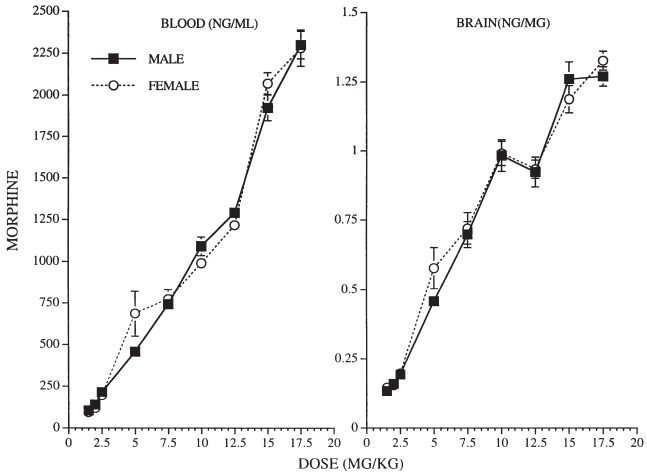

FIG. 2. Mean (±SEM) blood (ng/ml) and brain (ng morphine/mg protein) in male and female rats injected with 1.5 to 17.5 mg/kg morphine subcutaneously 60 min prior to sacrifice (n = 10–15 at each dose). There are no statistically significant differences between males and females at any dose.

levels attained at doses in which maximal differences were observed in morphine's reinforcing properties. In agreement with results reported previously (11,12), there were also no gender-related differences in blood and brain levels of morphine at 15 or 30 min after its administration and, hence, these data are not reported here.

DISCUSSION

The results of these studies demonstrate significant sex-related differences in the positive reinforcing properties of morphine. Although morphine served as a positive reinforcer in both males and females, the dose–response curves were markedly different. At doses from 0.2 to 10.0 mg/kg, morphine induced a strong preference for the drug-associated chamber in both males and females, but as the dose was increased from 10–17.5 mg/kg, the preference for the drug-associated chamber declined sharply in males, whereas in females a very strong preference was still observed at doses up to 30 mg/kg. This pronounced sex-related differences in the upper dose at which morphine retained its positive reinforcing properties is probably understated by the results shown in this article. Specifically, we could not find any dose in females that failed to generate a clear preference for the morphine-associated chamber, because significant lethality occurred at doses in excess of 30 mg/kg. Hence, the difference between males and females in the highest dose of morphine that might engender a preference for the drug associated chamber is at least twofold. Because we found no gender-related differences in the blood and brain levels of morphine during the 60-min period used in the conditioning phase (Fig. 2), it seems reasonable to conclude that there are intrinsic sex-linked differences in the sensitivity of those brain regions mediating the positive reinforcing properties of morphine.

The present observations extend previous work from this and other laboratories that have shown large sex-related differences in morphine's antinociceptive activity (2,5,11,12, 22,24), and its discriminative stimulus properties (13,14). Our results seem to be one of the first to demonstrate that there are gender-differences in the positive reinforcing properties of morphine. Although there have been several reports in the human literature of sex-related differences in the subjective effects and abuse liability of psychoactive drugs, such as cocaine, other stimulants, and alcohol (3,9,17,25–28), we are unaware of any reports in which gender differences in the abuse liability of opiates have been examined in humans. There is a similar paucity of data in the preclinical literature. In fact, we are aware of only one study in which this issue has been examined.

Interestingly, Stewart et al. (31) found no significant differences between male and female rats in heroin self-administration, either in terms of dose–response characteristics or the maximal fixed-ratio schedule of reinforcement at which self administration ceased (i.e., break point). It is unclear why we observed large gender-related differences in the dose-response characteristics of morphine in a place-conditioning paradigm, but Stewart et al. (31) observed no differences at all in self-administration. These observations could indicate that place preference and self-administration measure different aspects of reinforcement that are sex dependent, or it is possible that, in fact, there may be no discrepancies in our data at all. Specifically, we only detected differences in morphine's reinforcing effects at very high doses that were not used in the self-administration paradigm employed by Stewart et al (31). Hence, it is not clear that these observations indicate significant discrepancies between the two methods used for assessing the reinforcing properties of opiates. Certainly, additional studies are required to more firmly establish whether differences exist in the reinforcing or rewarding aspects of the opiates utilizing a variety of experimental paradigms.

It should be stressed that the primary gender differences we observed was in the dose–response characteristics of morphine's reinforcing properties in the place-conditioning paradigm. Clearly, these data do not necessarily indicate that morphine is either more or less reinforcing or rewarding in males and females. Rather, they simply indicate that morphine induces a preference for the drug-associated chamber in females over a much broader dose range than in males, and that there are substantial differences in the maximum dose at which a preference can still be observed in females relative to males. This difference probably cannot be explained by gender-related differences in the ability to detect morphine, because the drug was found to serve as a positive reinforcer in males and females at comparable, very low doses, and equivalent blood and brain levels of morphine were achieved during the conditioning phase. In addition, previously it has been shown (14) that morphine served as a discriminative stimulus at much lower doses in females than in males reinforcing the conclusion that, at the very least, the ability to detect morphine did not play any role in the effects we observed in the place conditioning paradigm.

The previous discussion of sex difference in the discriminative stimulus properties of morphine, its antinociceptive effects, and reinforcing properties highlights an important aspect of sex differences in opiate pharmacology. Specifically, the direction of the difference between males and females is quite different, depending upon which aspect of morphine's pharmacology is assessed: (a) females require much larger doses of analgesics than do males (2,5,11,12,22,24) suggesting that they are less sensitive to morphine's effects than males; (b) in drug discrimination trials with opiates, females appear to be much more sensitive to their discriminative stimulus properties than males; and (c) in a place-conditioning paradigm, females appear to show similar place preference as

males at similar low doses, but—in marked contrast to males—continue to express a preference at very high, near-toxic levels of morphine. It is not immediately obvious how these differences in the sensitivity of morphine relate to one another and what light they shed on the mechanism underlying the important sex differences that have been observed. Clearly, additional studies are required to more fully understand the full and apparently very complex profile of sex differences in the pharmacology of the opiates and the mechanisms that underlie these differences.

The differences we have observed in the place-conditioning paradigm could be due to sex-related differences in the strength of morphine as a positive reinforcer or, conversely, an enhanced sensitivity to morphine's negative side effects at high doses in males. For example, it is feasible to suggest that the sex difference we observed could be related to several factors unrelated to the intrinsic rewarding properties of morphine: first, females may show a greater inherent "tolerance" to the adverse effects of morphine at higher doses than do males; second, males may have experienced a much stronger sedative or cataleptic response to morphine during the training phase such that they failed to associate the appropriate chamber with morphine; or, third, morphine may have actually disturbed the Pavlovian conditioning process in males, but not in females. Place-conditioning paradigms do not permit a resolution of these alternative explanations, but it is clear from our studies that morphine induces a preference for the drug-associated chamber at much higher doses in females than in males, regardless of which explanation is correct.

Whether the results of the place-conditioning studies described in this article have relevance to the reinforcing or rewarding properties of morphine is open to some debate. Although many theorists believe that a preference for the morphine-associated chamber in a place-conditioning paradigm reflects its rewarding properties (10,30) other investigators (32) would argue that these measures do not necessarily reflect reward. The recent observations by Stewart et al. (31) that there are no apparent differences in heroin self-administration in males and females, in contrast to our observations utilizing place preference, certainly adds fuel to this debate. However, once again—given the limited data set currently available—it would be unwise to draw any definitive conclusions regarding gender differences in the reinforcing or rewarding properties of morphine, pending the outcome of additional studies.

The mechanisms underlying the sex-related differences observed in the present studies are unknown. However, if one makes the logical assumption that these differences are in some manner due to differences in CNS sensitivity to morphine, one reasonable hypothesis is that there are differences between males and females in the density or affinity of those opioid receptors involved in mediating the reinforcing properties of morphine or the biochemical reactions triggered by receptor occupancy. While we are unaware of any data suggesting sex-related differences in opioid receptor profiles in those areas thought to mediate morphine's reinforcing properties, a number of earlier studies have suggested differences in the density of opioid receptors in so-called sexually dimorphic regions in males and females (18–21). However, it should be noted that these differences are restricted to a few discrete loci and that, in most important respects, the opiate receptor profiles in the male and female rat brain are remarkably similar (18–21). Thus, it is questionable that difference exist in the density or affinity of opioid receptors in males and females, which could explain the very large sex differences we have found in the reinforcing properties of morphine.

An additional somewhat obvious explanation of sex-related differences in the positive reinforcing properties of morphine is that sex steroids may mediate these effects. There are two mechanisms by which sex steroids could mediate gender-based differences in the response to morphine: acute "activational" effects (1,33,34); and, perhaps more importantly, long-term organizational effects that mediate sexual differentiation of brain morphology and neurobiology at the very late pre-natal or early postnatal period (1,7,8,15). At present, there is no evidence that either of these mechanisms could be involved in the sex-related differences we have observed.

On the basis of the preceding discussion of the possible mechanisms that could be involved in the sex-related differences we have observed in the positive reinforcing effects of morphine, it is apparent that, although some obvious factors are apparently not involved (e.g., pharmacokinetic differences or gross differences in opioid receptor profiles), we can offer no reasonable explanation at this time for this gender-related difference. Similarly, others have concluded that the previously observed gender differences in morphine-induced antinociception (2,11,12,22,24), or morphine's discriminative stimulus properties (13,14) cannot be readily explained at this time. Rather, at this point, it seems clear that large differences between males and females can be observed in many aspects or morphine's pharmacology, but that the mechanisms involved are unclear. Obviously, additional studies are required to examine the mechanisms that might be involved and, in a more general sense, to assess generality of these effects and their relevance to the abuse liability of the opiates.

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