ELSEVIER

Pharmacology Biochemistry and Behavior, Vol. 53, No. 2, pp. 433–435, 1996

0091-3057/96 $15.00 + .00

0091-3057(95)02013-Y

Male/Female Comparison of Morphine Effect on Food Intake—Relation to Anorexia Nervosa

MARY ANN MARRAZZI,[1] ALFRED McQUARTERS, CHARMAINE BARNES, JAWANA LAWHORN AND QUIN D'AMICO-RASMUSSEN

Department of Pharmacology, Wayne State University, School of Medicine, 540 E. Canfield, Detroit, MI 48201

Received 13 August 1992

MARRAZZI, M. A., A. McQUARTERS, C. BARNES, J. LAWHORN AND Q. D'AMICO-RASMUSSEN. *Male/female comparison of morphine effect on food intake—relation to anorexia nervosa.* PHARMACOL BIOCHEM BEHAV 53(2) 433–435, 1996.—We have proposed that endogenous opioids play a critical role in the etiology of anorexia nervosa by mediating an auto-addiction. A biological predisposition may result from an atypical endogenous opioid system. Morphine activation of the system increases food intake in most species, including normal humans and rats, but decreases food intake in mice. The atypical opioid system in mice may be representative of that in anorexia nervosa patients, causing the biological predisposition. Anorexia nervosa is 10 times more prevalent in females than males. In the context of this auto-addiction opioid model, it was interesting to determine if the effects of morphine on food intake were markedly different between the two sexes. Full dose-response curves were done of the effects of morphine on food intake in males and females in both rats and mice, representing the typical and atypical responses, respectively. Differences between the sexes were not found to explain the marked prevalence of anorexia nervosa for females. The marked preference is probably at some other step.

Morphine Opioids Mice Rats Food intake Anorexia nervosa Female Male Sex
Addiction Auto-addiction Atypical opioid systems Eating disorders

MARRAZZI and Luby have proposed an auto-addiction opioid model of anorexia nervosa in which endogenous opioids play a critical role (3,4). An initial period of dieting releases endogenous opioids that cause a positively reinforcing elation or high and an addiction to dieting. Although opiates are known to increase food intake, they may also adapt the organism to conserve energy in the face of starvation. If these opioid responses are uncoupled, addiction could occur to either, resulting in anorexia nervosa (addiction to the adaptation to starvation) or bulimia (addiction to the drive to eat). According to this hypothesis, interruption of the addictive cycle by opiate blockade with narcotic antagonists could be useful in the treatment of these eating disorders. Our initial clinical studies suggest this to be a very promising new approach to treatment (2,4,5,7).

Such uncoupling may occur when there is an atypical endogenous opioid system, resulting in a biological predisposition. In such individuals, dieting triggers an addiction, whereas for most it does not. In most species, including rats and normal humans, morphine activation of the endogenous opioid system increases food intake and causes sedation [see (1, 3,4,8) for further references]. In contrast, in female BALB/C mice, morphine decreases food intake and increases motor activity. These symptoms are seen in anorexia nervosa and are responses opposite to those of most species. We have suggested that the atypical opioid system in mice may be representative of that in an individual with a biological predisposition to anorexia nervosa or bulimia. Activation of such an endogenous opioid system by dieting may result in an addiction for that individual (1). Studies with a number of different mouse strains have demonstrated three patterns of atypical opioid systems—all of which could result in such a biological predisposition. Morphine activation can result in anorexia with hyperactivity, anorexia without hyperactivity, and a biphasic pattern of increased food intake at low doses and anorexia with hyperactivity at higher doses (8).

Anorexia nervosa is about 10 times more prevalent in females than males (3,4). In the context of our opioid mediated auto-addiction hypothesis, the question arises if the sex preference could be in the response to morphine. Sex differences in the levels and sensitivity of the endogenous opioid system and effects of gonadal hormones on the opioid system are known (3,4). Differences in the effect of morphine on food intake is one possible site of the sex differential. Accordingly, the

[1] To whom requests for reprints should be addressed.

morphine effects on food intake were compared in both sexes in both rats and mice—the typical and atypical opioid systems. Preliminary results have appeared (6).

METHOD

Sprague-Dawley rats from Charles River and BALB/C mice from Dr. Helene Rauch's colony derived from Jackson Labs were used as in our previous reports (1,8). The methods and calculations are the same as those previously described for the BALB/C mice (1). The lighting cycles was 12 h on, 12 h off. Morphine or normal saline (n-saline) was administered subcutaneously in the doses indicated 5 min before the beginning of the test period. A 4-h test period from 0900 to 1300 h was used. Because rodents are nocturnal, this is a time of minimal baseline feeding and activity. For each population of animals, all groups were shown to give the same values when injected with saline on at least three repeated tests, before proceeding with morphine. Each animal was tested with morphine maximally once in 3 weeks, which we previously demonstrated does not alter the response to morphine, i.e., does not cause physical dependence or tolerance.

Food intake was measured as the difference in the weight of Purina Laboratory Chow pellets made available at the beginning and still remaining at the end of the test period. Care was taken to correct for spillage. Food intake was measured to the nearest 0.01 mg on a Mettler P1200 balance. Two morphine groups (at two different doses) and one saline control group were done in each run. Values are expressed as the percent of simultaneously run controls, i.e., the mean of the experimental minus the mean of the control group divided by the latter and multiplied by 100. Using SPSS 4.0 for the McIntosh computer, repeated measures MANOVA was used to test for gender differences in the overall dose-response curves and the interaction of gender with the morphine effect. Simple effects t-tests were used to test for gender differences at specific doses when the interactions were significant, which is the equivalent of an F-test with only two groups.

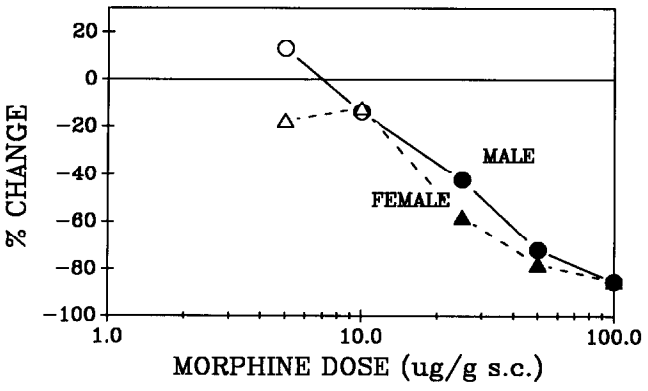

FIG. 1. Morphine effects on food intake in mice. Morphine was dosed on a per gram of mouse basis. The circles are male and the triangles are female. Solid symbols represent points for which food intake in the morphine group is statistically significantly different than the n-saline control group ($p < 0.01$), based on a t-test. There were 14–15 animals per group. Control values for food intake were 0.7–1.2 g for males and 0.5–1.2 g for females. Body weights were 35.2 ± 0.8 g for males and 27.8 ± 0.9 g for females. On simple t-tests, gender differences were significant at 5 μg/g, $F(1, 28) = 1.11$, $p < 0.002$, and 25 μg/g, $F(1, 28) = 2.02$, $p < 0.04$, doses.

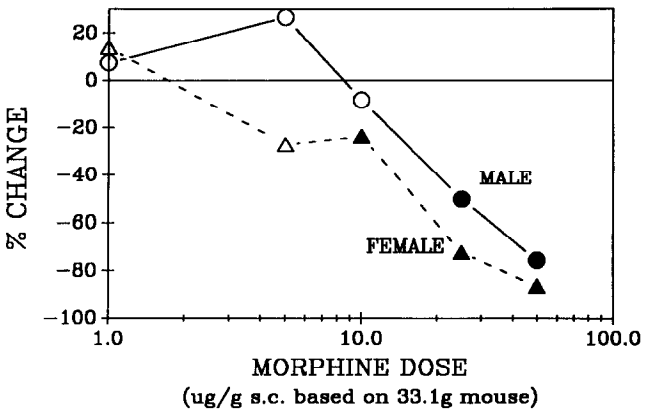

FIG. 2. Morphine effects on food intake in mice. Same as Fig. 1 except that morphine was dosed per mouse, based on a 33.1 g mouse. Control values for food intake were 1.0–1.4 g for males and 1.0–1.3 g for females. Body weights were 35.2 ± 0.8 for males and 27.8 ± 0.9 g for females. On simple t-tests, gender differences were significant at the 5 μg/g, $F(1, 28) = 5.07$, $p < 0.0001$, and 25 g/g, $F(1, 28) = 1.58$, $p < 0.005$, doses.

RESULTS

Figures 1–4 show the dose-response curves for morphine induced changes in food intake in mice and rats on a per gram and a per animal basis. Statistically sign curves: significant differences were found between genders for all dose-response curves: mice dosed per gram, $F(1, 28) = 7.89$, $p = 0.009$; mice dosed per animal, $F(1, 27) = 13.56$, $p = 0.001$; rats dosed per gram, $F(1, 27) = 8.02$, $p < 0.0001$; rats dosed per animal, $F(1, 27) = 12.50$, $p = 0.001$. Statistical significant interactions of gender and morphine effect were found for all curves except rats dosed per animal: mice dosed per gram-dose main effect, $F(4, 112) = 104.25$, $p < 0.0001$, interaction,

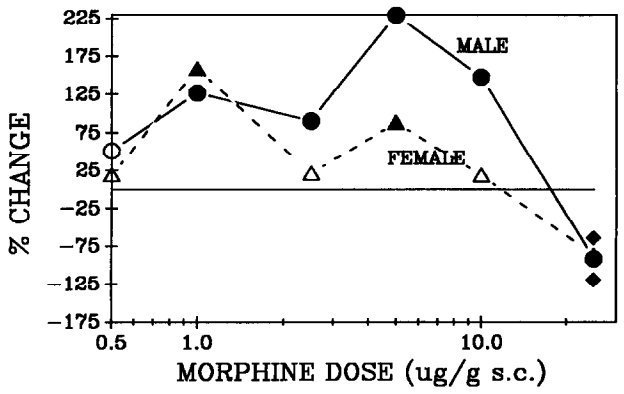

FIG. 3. Morphine effects on food intake in rats. Morphine was dosed on a per gram of rat basis. Same as Fig. 1. The diamonds mark the points for which the animals were so visibly sedated they could not eat. There were 14–15 animals per group. Control values for food intake were 1.3–4.3 g for males and 0.7–3.5 g for females. Body weights were 614.0 ± 15.3 for males and 377.3 ± 6.0 g for females. Simple t-tests showed gender differences at 2.5 μg/g, $F(1, 28) = 1.26$; $p = 0.002$, 5 μg/g, $F(1, 28) = 2.68$, $p = 0.001$, and 10 μg/g, $F(1, 28) = 1.86$, $p = 0.008$, doses.

$F(4, 112) = 3.41$, $p = 0.011$; mice dosed per animal-dose main effect, $F(4, 108) = 41.60$, $p < 0.0001$, interaction, $F(4, 108) = 3.19$, $p = 0.016$; rats dosed per gram-dose main effect, $F(5, 135) = 24.93$, $p < 0.0001$, interaction, $F(5, 135) = 3.82$, $p = 0.003$; rats dosed per animal, $F(5, 135) = 13.88$, $p < 0.0001$, interaction, $F(5, 135) = 1.52$, $p = 0.186$.

DISCUSSION

Although gender differences were shown, they are so small (less than twofold) that it is unlikely that sex differences in this response to endogenous opioids would account for the 10-fold greater susceptibility of females than males to anorexia nervosa. Moreover, the interpretation is complicated by the males weighing more (30–60%) than the females of the same age. The relevant distribution of morphine is not known. If the distribution is dependent on the body weight, it should be dosed per gram of animal. If it is a compartment independent of body weight, it should be dosed per animal. Matching animals by body weight would result in age differences. Dosing per body weight if it should be dosed per animal would result in a higher effective dose for the males and hence could result in a greater effect in males. Such a qualitative effect was seen in the rats, but a similar small effect was seen when dosed per body weight. However, the response in rats is the increase in food intake typical of most species rather than the decrease suggested to result in a biological predisposition to anorexia nervosa. In mice, where the decrease in food intake is seen, the female was slightly more responsive than the male. This was true only when dosed per animal. On a per weight dosing, this would be a slightly lower dose for the male, which would tend to magnify the effect. Nevertheless, while this effect was in the right direction, it was so small (less than twofold), that the significance in producing the 10-fold greater susceptibility of the female to anorexia nervosa is extremely doubtful.

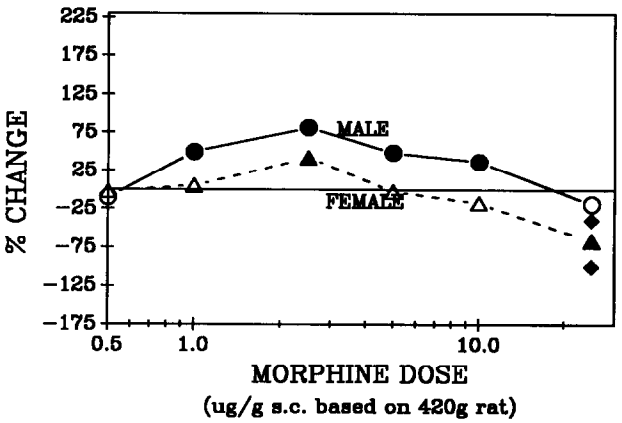

FIG. 4. Morphine effects on food intake in rats. Same as Fig. 3 except that morphine was dosed per rat, based on a 420 g rat. Control values for food intake were 3.0–4.5 g for males and 2.8–5 g for females. Body weights were 677.6 ± 17.6 g for males and 430.0 ± 11.9 g for females. Simple t-tests showed gender differences at 1 μg/g, $F(1, 28) = 1.29$, $p < 0.035$, 5 μg/g, $F(1, 28) = 1.46$, $p < 0.016$, 10 μg/g, $F(1, 28) = 1.15$, $p < 0.007$, and 25 μg/g $F(1, 28) = 3.35$, $p < 0.01$ doses.

Hence, the greater susceptibility of the female to anorexia nervosa is probably at another step.

ACKNOWLEDGEMENTS

We thank Elaine Hockman, Ph.D., of Wayne State University Research Support Laboratory for statistical consultation. This work was supported by NIH Grant #RR8167-10.

REFERENCES

1. Buck, M.; Marrazzi, M. A. Atypical responses to morphine in mice: A possible relationship to anorexia nervosa? Life Sci. 41: 765–773; 1987.
2. Luby, E. D.; Marrazzi, M. A.; Kinzie, J. Case reports—Treatment of anorexia nervosa with opiate blockade. J. Clin. Psychopharmacol. 7:52–53; 1987.
3. Marrazzi, M. A.; Luby, E. D. An auto-addiction opioid model of chronic anorexia nervosa. Int. J. Eating Disord. 5:191–208; 1986.
4. Marrazzi, M. A.; Luby, E. D. The neurobiology of anorexia nervosa: An auto-addiction. In: Cohen, M.; Foa, P., eds. The brain as an endocrine organ. New York: Springer Verlag; 1990:46–95.
5. Marrazzi, M. A.; Bacon, J. P.; Kinzie, J.; Luby, E. D. Naltrexone use in the treatment of anorexia nervosa and bulimia nervosa. Int. Clin. Psychopharmacol. 10:163–172; 1995.
6. Marrazzi, M. A.; Barnes, C.; Lawhorn, J.; D'Amico-Rasmussen, Q. Male/female comparisons of morphine effects on food intake—Relationship to an auto-addiction opioid model of anorexia nervosa. FASEB J. 4:A943; 1990.
7. Marrazzi, M. A.; Kinzie, J.; Luby, E. D. A detailed longitudinal analysis on the use of naltrexone in the treatment of bulimia. Int. Clin. Psychopharmacol. 10:173–176; 1995.
8. Marrazzi, M. A.; Mullings-Britton, J.; Stack, L.; Powers, R. J.; Lawhorn, J.; Graham, V.; Eccles, T.; Gunter, S. Atypical endogenous opioid systems in mice in relation to anorexia nervosa. Life Sci. 47:1427–1435; 1990.