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Sex and Day-Night Differences in Opiate-Induced Responses of Insular Wild Deer Mice, *Peromyscus maniculatus triangularis*

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KAVALIERS, M AND D G L INNES *Sex and day-night differences in opiate-induced responses of insular wild deer mice*, Peromyscus maniculatus triangularis PHARMACOL BIOCHEM BEHAV 27(3) 477–482, 1987 —We examined the effects of mu and kappa opiate agonists on the day- and night-time nociceptive, locomotory and ingestive behaviors of an island population of wild male and female deer mice, *Peromyscus maniculatus triangularis* The prototypical mu opiate agonist, morphine, had significant analgesic and locomotory effects, which were blocked by naloxone, and the specific delta opiate antagonist, ICI 154,129, respectively The specific kappa opiate agonist, U-50,488, had significant analgesic actions and inhibitory effects on locomotor activity, as well as stimulating feeding Significant day-night variations occurred in the analgesic and activity responses, with the mu and kappa opiate agonists having significantly greater effects at night There were also prominent sex differences in responses, male deer mice displaying significantly greater levels of mu and kappa opiate-induced analgesia and alterations in activity than female animals These sex differences in opiate-induced effects were most pronounced at night, female deer mice displaying reduced day-night rhythms of responsiveness These results demonstrate the existence of significant day-night rhythms and sex differences in the mu and kappa opiate behavioral responses of a wild population of rodents

Analgesia Locomotor activity Feeding Deer mouse *Peromyscus maniculatus* Mu opiate Kappa opiate Sex differences Day-night rhythm Island

THERE is substantial evidence that endogenous opioid systems participate in the regulation of basic behavioral and physiological functions Results of investigations with laboratory mice *(Mus musculus)* and rats *(Rattus rattus)* have revealed the existence of multiple endogenous opioid peptides and differing opioid receptors [24] Data has been further presented to show that agonists and antagonists affecting delta, kappa, mu and sigma opiate receptors can have marked influences on the analgesic, feeding, locomotory and related behaviors of most animals, including mice, rats and laboratory bred populations of deer mice, *Peromyscus maniculatus* [7, 17–22, 25, 30, 35] The opiate mediated responses of laboratory mice and rats have been shown to display prominent day-night rhythms with peak nocturnal sensitivity [4, 17–19, 25, 31, 34] There is also evidence for sexual differences in opioid systems and sensitivity to exogenous opiates, with females generally displaying lower opioid activity and responses than males [1–3, 6, 14–16, 21, 28, 33, 37] Opioid involvement in the determination of the behavioral and physiological responses of wild rodents has, however, received minimal attention Furthermore, whether or not there exist day-night and sex differences in the opiate-mediated responses of wild rodents has also not been established

Islands off the coast of British Columbia, which have been isolated from the mainland since at least the last glacial period approximately 12,000 years ago [32], contain numerous subspecies of *P maniculatus* These insular deer mice, as well as other island populations of mammals are suggested to differ in a number of their behavioral, ecological and morphological characteristics from mainland populations [10, 12, 13] Thus, analysis of the opioid systems of wild insular rodents is of ecological as well as pharmacological and neurochemical interest

In the present study, we describe the effects of the prototypic mu opiate agonist, morphine [24], the highly specific kappa opiate agonist, U50,488H [36], the prototypic mu opiate antagonist, naloxone [24] and the delta opiate antagonist, ICI 154, 129 [11], on the day- and night-time nociceptive and locomotory responses of a wild population of large male and female deer mice, *Peromyscus maniculatus triangularis*, from a small island off the northern tip of Vancouver Island We also report the effects of the mu and kappa opiate agonists on the day- and night-time food intakes of male deer mice from this insular population

METHOD

Animals

Sexually mature male and female deer mice, 30–70 g and

approximately two years of age, were housed either singly or in pairs in polyethylene cages provided with cotton bedding at 21±1°C under a 20 hr light 4 hr dark cycle During experimental determinations the deer mice were held under a 12 hr light 12 hr dark cycle Food (Purina Rat Chow 5015) and water were provided ad lib Mice were live-trapped on Triangle Island (50° 47′ N 129° 05′ W and approximately 4 km² in area), about 48 km northwest off Cape Scott on Vancouver Island

Experimental Procedures

Nociceptive and activity determinations At either the mid-light or the mid-dark period mice (n=10, 5 males and 5 females) received intraperitoneal (IP) injections of either morphine (0 10, 1 0 and 10 mg/kg, B D H , Canada), U-50,488H (0 10, 1 0 and 10 mg/kg, UpJohn, MI) or the saline vehicle (10 ml/kg) Prior to day-time injections with morphine (1 0 mg/kg) and U-50,488 (1 0 mg/kg), and at 15–120 minute intervals afterwards, total locomotor activity displayed over 1 minute was recorded (Varimax Activity Meter, OH) for individual mice, followed by determinations of the latency of their foot-licking responses to an aversive thermal stimulus (50±0 5°C hot-plate, Omni-Tech, OH) The nociceptive and locomotory effects of the other doses of the opiate agonists were examined 30 minutes after IP administration In addition, the effects of pretreatment with either naloxone (1 0 mg/kg, Sigma, MO), ICI 154,129 (10 mg/kg, ICI, England) or saline on the day-time locomotory and nociceptive effects of morphine (10 mg/kg) were examined 30 minutes after injection (n=5 males, in all cases) In control determinations it was established that the activity measurements had no evident effects on the nociceptive responses of deer mice Dark period determinations were carried out under a dim red light As an individual deer mouse was subject to more than one treatment, the order of the manipulations was counterbalanced

This entailed systemically varying the presentation of the high and low doses of the agonists to prevent any ordering effects, with a minimum of 4 days between treatment of any animal The male and female deer mice that were being tested were randomly selected This procedure was necessary because only a limited number of these wild animals were available Control determinations with saline and morphine (10 mg/kg) showed that the manipulations and testing procedures had no evident effects on the thermal response latency and locomotory responses of the deer mice to either the agonists and antagonists, or on their basal behaviors

Food intake determinations Deer mice were housed individually in elevated 20 cm diameter (7 cm high) clear plastic small rodent metabolism units that had a wire mesh floor (E-1100 Econo-Metabolism Unit, Maryland Plastics, NY) Cotton bedding was provided for the animals in the feeding units A short (3 cm) aluminum tunnel provided access to a food hopper in which powdered food (Purina Rat Chow 5015) was placed An aluminum ring in front of the hopper restricted entry to only the head and prevented the animals from placing their feet in the food The animals readily consumed the powdered food by licking Water was provided in a plastic, graduated tube which was placed directly across the unit from the food hopper

After 1–2 days of habituation, the animals were provided with pre-measured amounts of food (2 0–2 5 g) in a plastic tray in the food hopper The amounts eaten by licking were determined by weighing the residual powder to the nearest

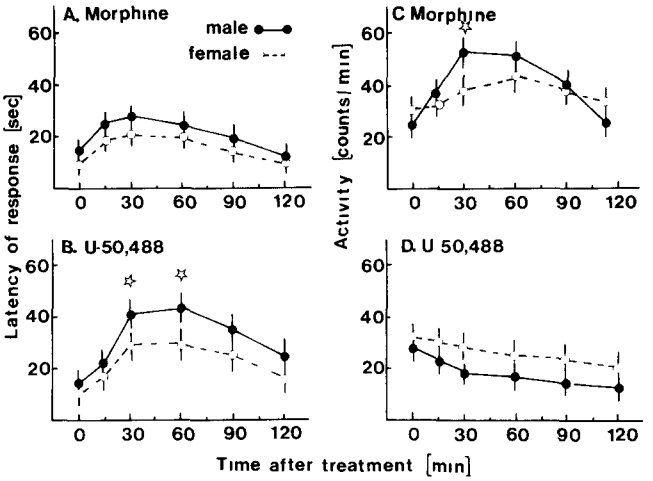

FIG 1 Time courses of the effects of intreperitoneally administered morphine sulfate (1 0 mg/kg, A,C) and U-50,488 (1 0 mg/kg, B,D) on the thermal response latencies and locomotor activity levels of male (●) and female (○) deer mice N=5 in all cases Vertical lines denote two standard errors of the mean Stars denote significant ($p<0$ 05) sex differences

0 01 g at hourly intervals Food that was lost by scatter or spillage (0 01–0 03 g) was collected and weighed Determinations were made on the amounts of food ingested by mice (n=5, males) hourly, in three-hour blocks in the light (1200–1500 hr) and the dark (2100–2400 hr) periods following IP injections of either morphine sulfate (10 mg/kg) or U-50,488H (1 0 mg/kg) In addition, the effects of naloxone (1 0 mg/kg) pre-treatment (n=5) on the ingestive responses to U-50,488H were examined in the light period The doses of the mu and kappa agonists used were based on the results of previous studies with laboratory populations of deer mice [24]

Data were analysed by analyses of variance and the Student-Newman-Keuls range test was used for aposteriori comparisons, with the significance level set at 0 05

RESULTS

Locomotory and Nociceptive Responses

The mu and kappa opiate agonists, morphine and U-50,488H, respectively, had significant ($p<0$ 05, for 1 0 mg/kg) day- and night-time locomotory and nociceptive effects in both male and female deer mice (Figs 1–3) Maximum responses were evident 30–60 minutes after administration

There were significant sex by dose interactions in day-and night-time morphine-induced analgesia, day, $F(3,42)=21$ 6, $p<0$ 01 This interaction shows the presence of significant dose-response relationships for morphine-induced analgesia, and that these responses differ between males and females In all cases, the thermal response latencies of animals treated with 1 0 and 10 mg/kg of morphine were significantly ($p<0$ 05) greater than those of the saline injected animals (Fig 2A) In addition, the analgesic responses of male mice treated with 10 mg/kg of morphine in the light period were significantly ($p<0$ 05) greater than those of animals receiving 1 0 mg/kg of morphine (Fig 2A) There were also marked male-female, $F(1,42)=19$ 9, $p<0$ 01, and day-night, $F(1,42)=15$ 3, $p<0$ 01, differences in the analgesic effects of morphine Morphine had a significantly ($p<0$ 01, for 10 mg/kg, light period and 1 0 mg/kg, dark period) greater

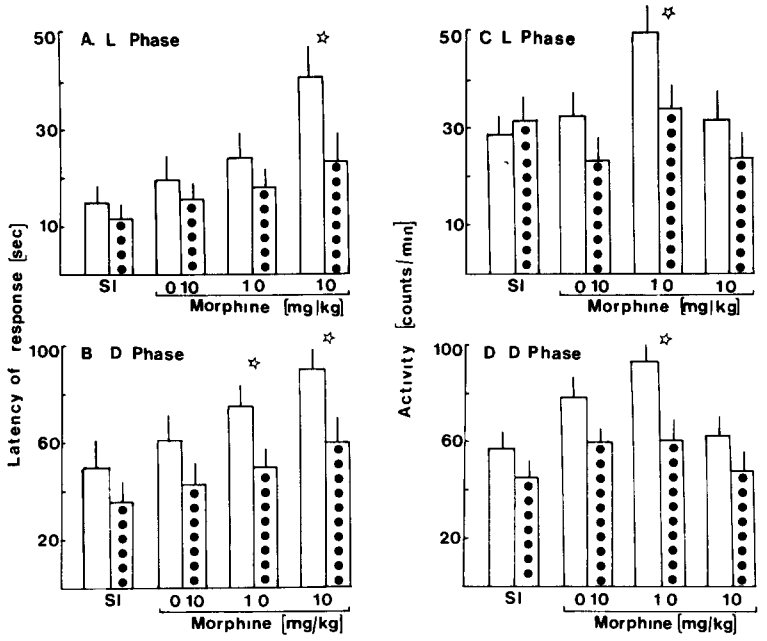

FIG 2 Day-night variations in the effects of intraperitoneally administered morphine (0 10, 1 0 and 10 mg/kg) and saline control (S1, 10 ml/kg) on the thermal response latencies and one-minute locomotor activity levels of male (open histograms) and female (●●●) deer mice Responses were determined 30 minutes after injections Stars denote significant ($p<0$ 05) differences in response between male and female deer mice N=5 in all cases Vertical lines denote two standard errors of the mean

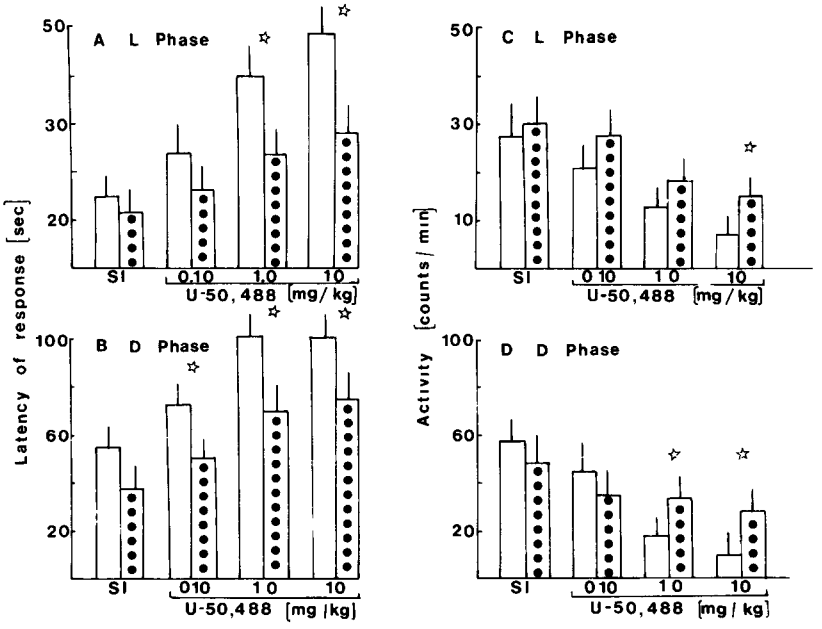

FIG 3 Day-night variations in the effects of intraperitoneally administered U-50,488 (0 10, 1 0 and 10 mg/kg) and saline control (S1, 10 ml/kg) on the thermal response latencies and one-minute locomotor activity levels of male (open histograms) and female (●●●) deer mice Responses were determined 30 minutes after administration Stars denote significant ($p<0$ 05) differences between males and females N=5 in all cases Vertical lines denote two standard errors of the mean

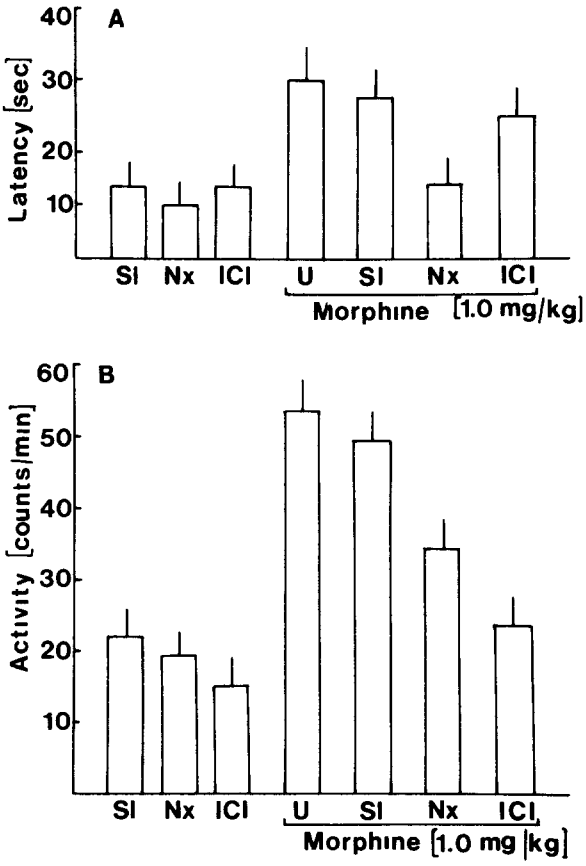

FIG 4 Effects of pre-treatment with either naloxone (Nx, 1 0 mg/kg), ICI 154,129 (ICI, 10 mg/kg) saline (10 ml/kg) or control handling (U) on (A) the thermal response latencies and (B) locomotor activity levels of male deer mice intraperitoneally injected with morphine (1 0 mg/kg) or receiving control handling Responses were determined 30 minutes after injection N=5 in all cases Vertical lines denote two standard errors of the mean

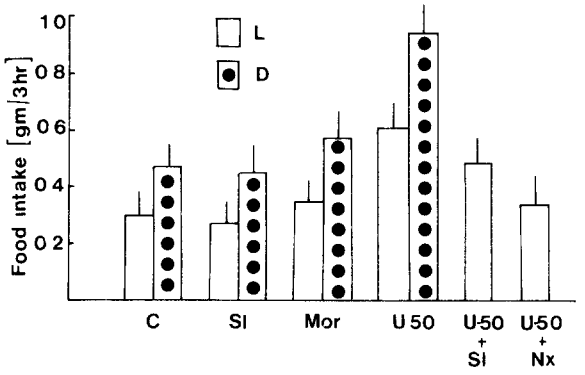

FIG 5 Effects of intraperitoneal injections of either morphine (Mor 1 0 mg/kg), U-50,488 (U-50, 1 0 mg/kg) saline (S1, 10 ml/kg) or control handing (C) on the mid-light (L) and mid-dark (D) period three-hour food intakes of male deer mice In addition, the effects of pre-treatment with naloxone (Nx, 1 0 mg/kg) and saline (S1, 10 ml/kg) on the mid-light ingestive responses of deer mice receiving U-50,488 (U-50, 1 0 mg/kg) are provided N=5 in all cases Vertical lines denote two standard errors of the mean

analgesic effect in male than in female deer mice (Figs 2A,B) Male deer mice displayed a non-significant, but greater, basal (saline) nociceptive response than female animals In all cases, the animals displayed significantly ($p<0$ 01) greater thermal response latencies and morphine-induced analgesia at night than in the day-time These night-time peaks were, however, significantly ($p<0$ 05 for 1 0 and 10 mg/kg morphine) lower in females than males (Fig 2B) Moreover, only the male deer mice displayed a significantly ($p<0$ 03) greater nocturnal response to morphine after correcting by subtraction for the elevated night-time basal response latency The deer mice also displayed significant, $F(1,42)=23$ 6, $p<0$ 01, day-night and male-female, $F(1,42)=18$ 4, $p<0$ 01, differences in their activity levels and locomotory responses to morphine (Figs 1C, 2B,D) In all cases, deer mice were significantly ($p<0$ 05) more active at night than in the day-time (Figs 2C,D), with the night-time locomotory responses of the morphine-treated female deer mice being significantly ($p<0$ 05) lower than those of the males In the day-time, morphine (1 0 mg/kg) significantly ($p<0$ 05) increased the activity of only the male deer mice (Fig 2C) At night, morphine (0 10 and 1 0 mg/kg) significantly ($p<0$ 01) increased the activity levels of male and female deer mice, with a significantly ($p<0$ 05) greater locomotory effect evident in the male animals (Fig 2D)

The day-time analgesic effects of morphine (1 0 mg/kg) were blocked by pre-treatment with the opiate antagonist, naloxone (Fig 4A) The delta opiate antagonist, ICI 154,129 slightly, and non-significantly, reduced morphine-induced analgesia Pre-treatment with saline control had no evident effects on morphine-induced analgesia In addition, naloxone and ICI 154,129 had no evident effects on the basal day-time thermal response latencies

Naloxone and ICI 154,129 also reduced the day-time locomotory effects of morphine (1 0 mg/kg) in male deer mice (Fig 4B) ICI 154,129 completely blocked the morphine-induced elevations in activity, while naloxone significantly ($p<0$ 05) reduced, but did not block, the elevated locomotory activity The inhibitory effects of ICI 154,129 were significantly ($p<0$ 05) greater than those of naloxone Saline pre-treatment had no evident effects on basal or morphine-induced activity In addition, naloxone and ICI 154,129 had no significant effects on basal activity

The kappa agonist, U-50,488 had significant ($p<0$ 05) day- and night-time analgesic effects in both male and female deer mice (Figs 1B, 3A,B) There were also significant day- and night-time sex by dose interactions in U-50,488-induced analgesia, day, $F(3,42)=18$ 7, $p<0$ 01 This indicates that there are significant dose-response relationships for the analgesic effects of U-50,488 and that these effects differ between the male and female deer mice In the day-time, U-50,488 caused significant ($p<0$ 05, for 0 10 mg/kg in males), dose-dependent elevations in thermal response latencies, with significantly ($p<0$ 05) greater analgesic responses evident in the males than in the females (Fig 3A) U-50,488 had significantly ($p<0$ 05) greater analgesic effects at night than in the day-time in both the male and female deer mice, $F(1,42)=26$ 5, $p<0$ 01 As with morphine, these analgesic effects were significantly, $F(1,42)=17$ 8, $p<0$ 01 greater in males than females In addition, U-50,488 had significantly ($p<0$ 05) greater analgesic effects than equivalent dosages of morphine

U-50,488 also affected the activity of the deer mice, significantly ($p<0$ 05) reducing the day- and night-time locomo-

tory levels The activity levels of the injected male mice were significantly ($p<0$ 05 for 10 mg/kg, light period and 1 0 and 10 mg/kg, dark period) lower than those of females The greatest differences between the activity responses of males and females to U-50,488 was present at night (Figs 3C,D)

Food Ingestion

Deer mice displayed day-night variations in their feeding responses, ingesting significantly ($p<0$ 05) greater amounts of food at night than in the day-time (Fig 5) Male deer mice receiving U-50,488 (1 0 mg/kg) displayed significant ($p<0$ 01) day- and night-time enhancements of food intake (Fig 5) Morphine (10 mg/kg) treatments had no significant effects on the ingestive responses on the deer mice Their ingestive responses were similar to those controls and saline treated animals Pre-treatement with naloxone significantly ($p<0$ 05) reduced, but did not completely block, U-50,488 augmented feeding Saline pre-treatments had no evident effects on the ingestive responses to U-50,488

DISCUSSION

The present results indicate that wild deer mice, *Peromyscus maniculatus triangularis*, possess functional opioid systems which are involved in the mediation of their analgesic, locomotory and ingestive behaviors in a manner comparable to that described for laboratory bred rodents [7, 18–20, 25] This study demonstrates that there exist significant male-female differences and marked day-night variations in mu and kappa opiate-mediated behavioral responses Moreover, these results describe the presence of significant sexual differences in the diel patterns of opiate sensitivity These results complement demonstrations of significant sex differences in endogenous opioid mediated stress-induced and exogenous opiate-mediated analgesia and other behavioral responses in laboratory bred populations of deer mice [16, 20, 21, 30, 35]

Morphine had significant analgesic and locomotory effects in both sexes The analgesic effects of morphine were blocked by the prototypic opiate antagonist, naloxone [31], and were insensitive to the relatively specific delta opiate antagonist, ICI 154,129 [11], whereas the locomotory effects of morphine were blocked by ICI 154,129 and only partially antagonized by naloxone In parallel investigations, it was observed that naloxone suppressed immobilization-induced analgesia in these deer mice, while ICI 154,129 inhibited the locomotory effects of restraint [21] This indicates that mu and delta opioid receptors are involved in modulating the nociceptive and locomotory responses, respectively, of wild deer mice in a manner similar to that described in other rodents [24] The kappa opiate agonist, U-50,488 [36], also had marked analgesic effects and significantly reduced the locomotor activity of the deer mice In preliminary studies, it was observed that the analgesic effects of U-50,488 were reduced by naloxone and ICI 154,129, while the alterations in activity could be partially antagonized by ICI 154,129 (unpublished) The latter observations are consistent with the recent suggestions obtained from studies with laboratory rodents that kappa and mu opiates may have opposing behavioral actions [27] The kappa agonist also had significant ingestive effects which were only partially antagonized by naloxone In contrast, morphine was relatively ineffective in stimulating food intake by the free-feeding deer mice These findings again agree with the results of investigations with laboratory populations of deer mice in which it was shown that kappa opioid systems were involved in the mediation of food ingestion, while mu and possibly other opioid systems affected food search and hoarding [20]

P m triangularis exhibited marked day-night variations in these opiate-mediated responses, displaying significantly greater analgesic, locomotory and ingestive response at night As deer mice are primarily night-active in the wild and under laboratory conditions [22,29], the nocturnal peaks in opiate sensitivity are consonant with their natural behaviors The presently described elevated night-time response of the deer mice to mu and kappa agonists also agree with the reponses of nocturnally active laboratory mice and rats Those rodents also displayed marked day-night rhythms in mu and kappa opiate-induced analgesia and feeding, with maximum responsiveness at night [4, 18–20, 34] There is biochemical evidence that the endogenous opioid systems of rodents undergo significant diel changes, with reports of greater numbers of opioid binding sites in the rat brain at night [17] Furthermore, it has been demonstrated that the opioid peptide dynorphin, which is an endogenous ligand for the kappa opioid receptor, shows a marked nocturnal increase in the hypothalamus of rats [31] The present results suggest that similar diel variations in opioid activity and opiate-medated responses occur in wild deer mice

In addition to the day-night rhythms in opiate sensitivity, there were also significant sexual differences in the opiate responses of the deer mice Male deer mice displayed higher levels of mu and kappa opiate mediated analgesia and locomotory activity changes than did the females Moreover, these male-female differences were at their maximum in the dark period, the nocturnal elevations in opiate sensitivity being markedly greater in males than in females Sex related differences in day-time response to noxious stimuli, morphine- and stress-induced analgesia have been previously reported in rats, with the females generally displaying lower response levels [1, 2, 28, 33] The present findings confirm these sexual differences in morphine-induced analgesia and extend them to a natural population Moreover, these results demonstrate that there exist sexual differences in responses to kappa as well as mu opiates As well, these findings show that there are prominent sexual differences in the day-night rhythms of opiate sensitivity, with females showing a reduced nocturnal responsiveness These observations point out the need to consider both day- and night-time responses when comparing opiate and other neurochemical effects in males and females

These sexual differences in opiate sensitivity may be modulated by gonadal steroids There is evidence that the analgesic responses of rats can vary across the estrous cycle, and it has been suggested that these responses may be sensitive to gonadectomy and steroid therapy [3] In addition, biochemcial studies have demonstrated that the levels of Met-enkephalin fluctuate as a function of the stage of the estrous cycle in the female rat [2, 3, 6] and that naloxone binding in the preoptic area varies with the stage of the estrous cycle [18,19] However, results of other studies have revealed no differences in opiate-mediated responses of mice across the estrous cycle [26] and that neither gonadectomy nor administration of gonadal steroids affect central opioid binding [9] The majority of the females in the present study were anestrous, minimizing the influences of gonadal steroid fluctuations, and reducing the variability in responses Whether or not the day-night patterns of opiate sensitivity of female deer mice and other animals vary across the estrous cycle remains, however, to be determined

Although the present results are consistent with previous investigations with mainland deer mice, demonstrating the presence of delta, kappa and mu opiate-mediated behavioral responses ([24, 25, 32] in preparation) there are a number of differences in the degree of sensitivity [16,21] It is possible that slight variations in the functioning of opioid systems could contribute to the behavioral and ecological differences evident between island and mainland populations of deer mice and other animals [10, 12, 13, 23] The rapid genetic selection [8] and apparently extensive protein polymorpism and genetic heterogeneity displayed by deer mouse populations [5] supports the likelihood of a divergence in the activity of opioid and other neurochemical systems in insular populations

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