Pharmacology Biochemistry & Behavior, Vol. 32, pp. 613–619. © Pergamon Press plc, 1989. Printed in the U.S.A. 0091-3057/89 $3.00 + .00

Population Differences in Benzodiazepine Sensitive Male Scent-Induced Analgesia in the Deer Mouse, *Peromyscus maniculatus*

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Received 14 July 1988

KAVALIERS, M. AND D. G. L. INNES. *Population differences in benzodiazepine sensitive male scent-induced analgesia in the deer mouse,* Peromyscus maniculatus. PHARMACOL BIOCHEM BEHAV **32**(3) 613–619, 1989.—We compared opioid and nonopioid involvement in the mediation of scent-induced analgesia in two populations of deer mice, *Peromyscus maniculatus; P. m. artemisiae* from a mainland region and *P. m. angustus* from a small marine island. Exposure to bedding taken from the soiled home cage of an isolated (dominant aggressive) male resident elicited a significant increase in the nociceptive responses of male deer mice from mixed sex pairs, with the island population of mice displaying significantly greater analgesic responses than the mainland animals. In the mainland population of mice, the large amplitude analgesia induced by the scent of a conspecific was insensitive to the opiate antagonist, naloxone, but could be blocked by either the benzodiazepine antagonist, Ro 15-1788, or agonist, diazepam. Exposure to the scent of individuals from the island population elicited a lower amplitude analgesia that was sensitive to both the opiate and benzodiazepine manipulations. In the island population, both the lower amplitude analgesia induced by the scent of a conspecific and the higher amplitude analgesic elicited by the scent of a mainland animal was blocked by naloxone and only partially reduced by the benzodiazepine manipulations. Bedding treated with the peppermint also induced analgesia, with the island mice displaying a markedly greater analgesic response than the mainland animals. In both populations of deer mice the peppermint-induced analgesia was blocked by naloxone and insensitive to the benzodiazepine manipulations. These findings are considered in terms of their possible ecological significance and relations to the differences in agonistic and social behaviors between island and mainland populations of deer mice and other small rodents.

Analgesia Scent Naloxone Benzodiazepine Ro 15-1788 Diazepam Deer mouse *Peromyscus maniculatus* Island-mainland populations

THE ability to respond to biological and physical stimuli is a basic characteristic of all animals. A broad variety of environmental factors are capable of inducing analgesia and rendering animals less responsive to aversive events (3). Recently, the ecological and ethological relevance of this stress-, or more appropriately, environmentally-induced analgesia, has come under consideration. In laboratory mice, *Mus musculus*, intraspecific agonistic encounters and subsequent defeat have been used to induce analgesia in the vanquished individual (18, 22, 28, 40). Depending on the strain of mouse used and characteristics of the encounter, either endogenous opioid or nonopioid mediated analgesia is evident. Protracted encounters lead to the induction of opioid analgesia (22,40), while relatively brief interactions in DBA/2 mice result in a nonopioid analgesia in the submissive individuals (29). The latter acute analgesia is insensitive to the prototypic opiate antagonist, naloxone, and does not show cross-tolerance to morphine (28,31), but apparently is sensitive to the irreversible opiate antagonist beta-chlorantrexamine (37).

This naloxone-insensitive analgesia, which is attenuated by a number of benzodiazepine agonists and antagonists, was initially proposed to be modulated by putative endogenous ligands for benzodiazepine binding sites (31). Recently, however, evidence has been presented suggesting that benzodiazepine recognition sites are not directly involved in the mediation of this nonopioid defeat-induced analgesia in DBA/2 mice (32–35). Nonopioid analgesia that is sensitive to benzodiazepine antagonists and agonists can also be induced in DBA/2 mice by exposure to just the soiled bedding (scent) of an isolated dominant male (45).

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Recently, a similar nonopioid, scent-induced analgesia was observed in male deer mice, *Peromyscus maniculatus*, that were briefly exposed to the olfactory cues associated with an isolated, dominant and potentially threatening male (21). These scent-induced analgesic responses were suggested to be part of ecologically adaptive, preparatory, defense response (21,30). As such, these responses are subject to natural selection and, thus, should reflect the specific social features, including levels of aggression and degree of intraspecific agonistic interactions, that are characteristic of a particular population.

Deer mice from various habitats and geographic areas have been shown to differ in a number of their behavioral, biochemical, ecological and morphological characteristics (1, 6, 8, 17, 19, 23, 25, 38). In particular, populations of deer mice and other small mammals inhabiting isolated islands (insular or island populations) exhibit significant differences in social and agonistic behaviors from their counterparts that are found on the mainland (mainland populations) (11, 25, 38). Reduced aggression towards potential territory holders and neighbors in insular rodents is suggested by the generally lower frequencies or intensities of aggressive encounters (23, 25, 26, 38, 39). In neutral arena experiments adult deer mice from small islands generally displayed less aggressive behavior towards conspecifics than did animals from the mainland (14). Moreover, adult insular deer mice showed little aggression towards unrelated juveniles, whereas mainland populations of adult deer mice were highly aggressive towards juveniles (13). These behavioral differences between island and mainland populations of deer mice and other small rodents have been attributed to both genetic and environmental factors (11).

Recently, we have presented evidence that some of the behavioral and ecological differences between both wild and laboratory bred island and mainland populations of deer mice may, in part, be related to differential activation and expression of endogenous opioid systems under both normal and stressful conditions (17,19). Whether or not island and mainland populations of deer mice also differ in their nonopioid, benzodiazepine sensitive, behavioral responses to aversive situations is not, however, known.

In the present study, we examined the effects of exposure to the scents of isolated [dominant/aggressive (5)] males, as well as exposure to a novel odor (peppermint), on the nociceptive responses of an island and a mainland population of male deer mice. In addition, we describe the effects of the prototypic opiate antagonist, naloxone, the benzodiazepine antagonist, Ro 15-1788 (14), and the benzodiazepine agonist, diazepam, on the olfactory-induced responses of the deer mice.

METHOD

Experimental Animals

Sexually mature male and female deer mice (*Peromyscus maniculatus angustus* and *P. m. artemisiae*, all 20–30 g, 2 months–1 year of age) were housed according to population (subspecies) either singly (males) (minimum of 2 weeks) or in mixed-sex pairs. The mice were held in polyethylene cages provided with cotton nesting material and Beta-Chip bedding at $21 \pm 1°C$, under a natural photoperiod (approximately 14 hr light:10 hr dark). Food (Purina Rat Chow 5012) and water were provided ad lib. *P. m. angustus* were derived from a population found on Morseby Island (48°N, 127°W, and approximately 5 km^2 in area in the Gulf Islands lying between the southern mainland of British Columbia and Vancouver Island). *P. m. artemisiae* were from a population trapped in the interior of British Columbia near Kamloops (50° 45′ N; 121° 30′ W). Various characteristics of the wild and laboratory populations are described elsewhere (12, 16, 17, 25).

Experimental Procedures

At approximately mid-photoperiod, male insular and mainland deer mice from mixed sex pairs (n = 12, in all cases) were placed individually in an unfamiliar cage ($27 \times 18 \times 13$ cm) with either: 1) clean bedding (150 ml of clean Beta-Chip), 2) the soiled (5-day-old) bedding (150 ml) of a different pair of deer mice from the same population, 3) the soiled (5-day-old) bedding of an isolated male deer mouse from either the island or mainland population, or 4) clean bedding to which a novel odor (0.5 ml of peppermint extract, Clubhouse, Ontario) was added.

After exposure for either 1 or 30 min to the soiled bedding of an isolated male, 5 or 30 min to the peppermint, or for 30 min to the other experimental conditions, the nociceptive responses of individual mice were determined. Nociception was measured as the latency of a foot-licking response to an aversive thermal stimulus ($50 \pm 0.5°C$ hot-plate, Omni-Tech). Thermal response latencies were recorded directly (0 min, 10–15 sec), 15, 30, 60 and 90 min after exposure to the stimuli, as well as 30 min prior to the manipulations. In an additional control procedure, the thermal response latencies of other mice (n = 12, for both populations) that received only handling were determined. The durations of exposure to the scents of the isolated males and various odors used were established in previous studies (21).

Either immediately before or directly after a 30-min exposure to either the soiled bedding of an isolated male, bedding treated with peppermint extract, or control handling, different groups of mice (n = 12, in all cases) received intraperitoneal injections of either naloxone hydrochloride (1.0 mg/kg/10 ml saline; Sigma), saline (10 ml/kg), diazepam (4 mg/kg/10 ml vehicle; Sigma), or Ro 15-1788 (10 mg/kg/10 ml vehicle; Hoffmann-La Roche) or the vehicle (10 ml/kg) of saline and several drops of Tween 80 (2 drops/10 ml). The doses of the benzodiazepine agonist and antagonist used were determined in previous investigations (21). Thermal response latencies of the mice receiving injections prior to the presentation of the novel cues were determined immediately after the exposure. Response latencies of the mice that were injected directly after exposure were determined 15 min later.

Data were analysed by analysis of variance and the Student Newman-Keuls test with the significance level set at 0.05.

RESULTS

Mice exposed to the soiled bedding of an isolated island or mainland male were analgesic, displaying significantly [$F(7,95) = 3.167$, $p<0.01$, for 30 min] greater thermal response latencies than mice placed in a cage with either clean bedding or animals just receiving handling (Figs. 1, 2). Exposure to the bedding of a conspecific mixed sex pair also had no evident effects on the thermal response latencies. There were no significant differences between the thermal response latencies of the island and mainland mice receiving control handling and exposure to either a clean substrate or the soiled bedding of a mixed sex pair. Exposure for 5 and 30 min to bedding with the novel odor of peppermint did, however, elicit significant, $F(3,47) = 4.39$, $p<0.05$, analgesic responses in both populations of deer mice (Fig. 3). In both populations, the levels of analgesia induced by exposure to the peppermint were similar to those obtained after 30 min of exposure to the soiled bedding of an isolated male from the mainland population (Figs. 2, 3).

The island and mainland populations of deer mice differed in their responses to the scents of isolated males. In the mainland

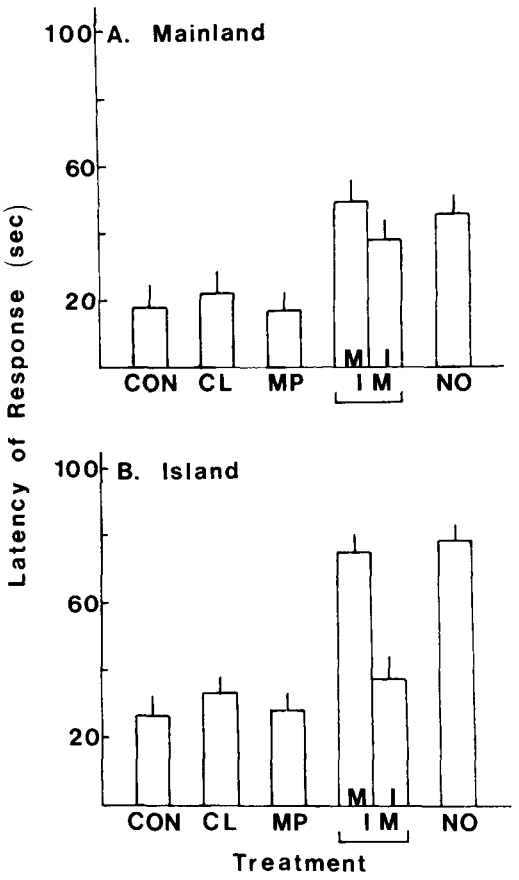

FIG. 1. Effects of 30 minutes of exposure to either the soiled bedding of an isolated male (IM) from an island (I) or mainland (M) population; the soiled bedding of a conspecific mixed sex pair (MP); bedding provided with the novel odor of peppermint (NO), or clean bedding (CL) on the thermal response latencies of male deer mice from two different populations. (A) *P. m. artemisiae* were from the mainland and (B) *P. m. angustus* were from a small island. The nociceptive response of mice from both populations that received control handling (CON) are also provided. N = 12, in all cases. Vertical lines denote a standard error of the mean.

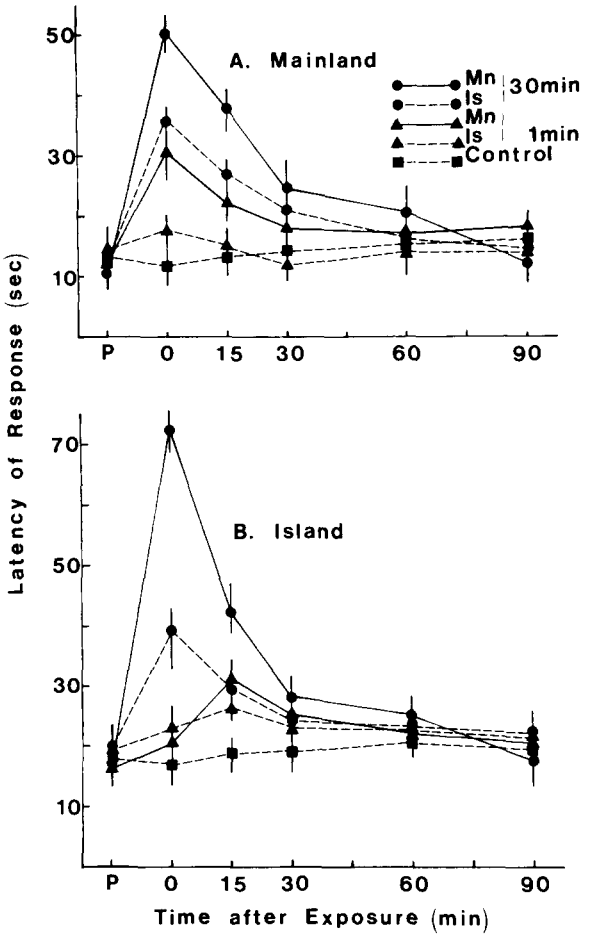

FIG. 2. (A–B) Effects of either 1 or 30 min of exposure to the soiled bedding of either an isolated male from the island (I) or mainland (M) population, or control handling, on the nociceptive response of male deer mice from two different populations. (A) *P. m. artemisiae* were from the mainland and (B) *P. m. angustus* were from a small island. The nociceptive responses of the animals 30 min prior (P) to the exposures or control handling are also shown. N = 12, in all cases. Vertical lines denote a standard error of the mean.

population, maximum analgesic responses were evident directly after exposure to the scent of an isolated male. A one-minute exposure to the scent of a conspecific mainland male induced an immediate, significant, $F(3,47)=3.86$, $p<0.05$, analgesic response that declined to preexposure levels by 15–30 min (Fig. 2A). A one-minute exposure to the scent of a male from the island population had no significant effects on the thermal response latency of the mainland animals. A 30-min exposure to the scent of a mainland male elicited a significantly, $F(2,23)=3.46$, $p<0.01$, greater amplitude and longer duration analgesic response than that obtained after the 1-min exposure. A 30-min exposure to the scent of an isolated island male also elicited a significant, $F(2,23)=4.64$, $p<0.01$, analgesic response. The amplitude of this latter response was, however, significantly, $F(2,23)=3.16$, $p<0.05$, lower than that observed following exposure to the scent of the conspecific.

In the island population, a one-minute exposure to the scent of a conspecific isolated male induced a significant, $F(3,23)=3.61$, $p<0.05$, analgesic response 15 min after exposure. The scent of the mainland male also induced a significant, $F(3,23)=3.85$, $p<0.05$, analgesic response that was significantly ($p<0.05$) greater than that induced by exposure to the conspecific (Fig. 2B). There were no significant changes in thermal response latency immediately after a 1-min exposure to either of the male scents.

A 30-min exposure to the scent of an island or mainland male also induced analgesia in the island population of deer mice. In this case, maximum analgesic responses were evident directly after exposure to the scent, with a return to basal levels by a further 30–60 min. The scent of the mainland animals elicited a markedly, $F(2,23)=3.94$, $p<0.01$, greater analgesic response than did that of a conspecific male. The analgesic responses induced by the former in the island population were significantly, $F(2,23)=3.41$, $p<0.05$, greater than those elicited in the mainland population.

Exposure to peppermint for either 5 or 30 min induced significant, $F(3,47)=4.62$, $p<0.01$, analgesic responses in both the island and mainland mice (Fig. 3). In each population, the degree of analgesia induced by the 30-min exposure was significantly, $F(2,23)=3.62$, $p<0.05$, greater than that evident after a 5-min exposure. The levels of analgesia were significantly [$F(2,23)=$

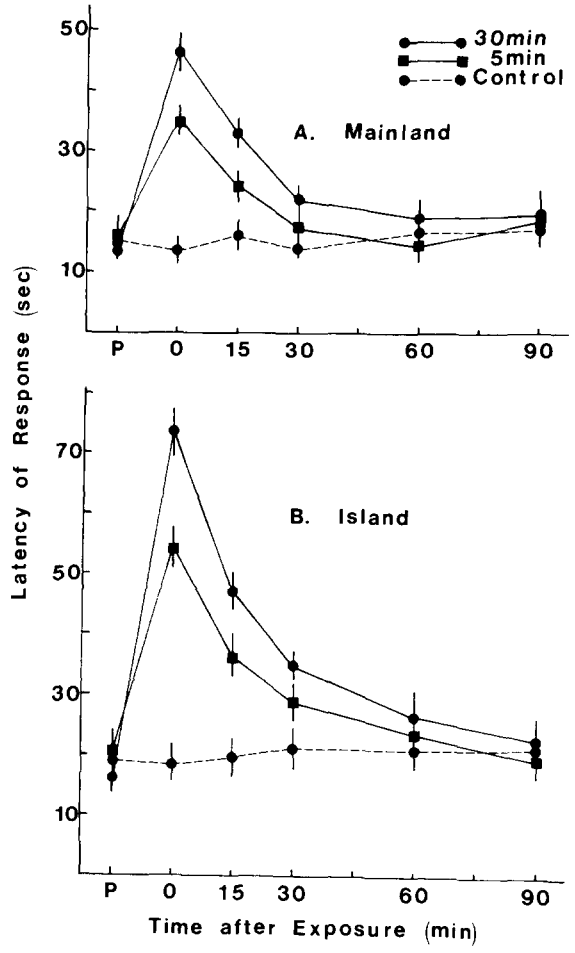

FIG. 3. (A–B) Effects of either 5 or 30 min of exposure to the peppermint, on the nociceptive responses of male deer mice from either the (A) mainland (*P. m. artemisiae*) or (B) an island (*P. m. angustus*). The nociceptive responses of the animals 30 min prior (P) to the exposure or control handling are also shown. N = 12, in all cases. Vertical lines denote a standard error of the mean.

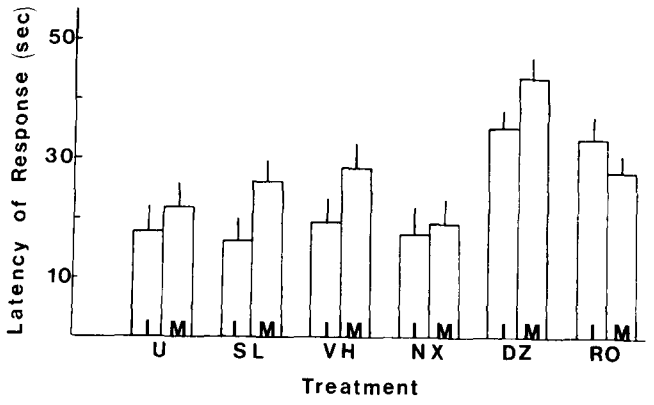

FIG. 4. Effects of treatment with either naloxone (NX; 1.0 mg/kg); diazepam (DZ; 4.0 mg/kg); Ro 15-1788 (RO; 10 mg/kg); vehicle (VH; 10 ml/kg) or handling without injection (U) on the thermal response latencies of either insular (I; *P. m. angustus*) or mainland (M; *P. m. artemisiae*) deer mice. Thermal response latencies were determined 30 min after injection. N = 12, in all cases.

2.84, $p<0.05$, for 5 min] greater in the island than in the mainland population. In both populations, the analgesic responses obtained after 30 min of exposure to the peppermint were similar in amplitude to those obtained after a 30-min exposure to the scent of an isolated male from the mainland population.

In the mainland population, the analgesia elicited by the scent of a conspecific male was blocked by preexposure injections of the benzodiazepine agonist, diazepam, and the benzodiazepine antagonist, Ro 15-1788 (Fig. 5A). Neither naloxone nor the vehicle treatments had any significant effects on the analgesic response. In contrast, the analgesia elicited by exposure to the island male was not significantly affected by the benzodiazepine treatments, but was blocked, $F(2,23)=3.26$, $p<0.05$, by naloxone. Vehicle treatment had no significant effects on this analgesic response. Previously, it has shown that pre- and postexposure injections of naloxone and the benzodiazepine agonist and antagonist had similar effects on the analgesic responses induced by exposure to the scent of a male conspecific (21).

In the island population, the analgesia induced by a male conspecific was blocked by the benzodiazepine agonist and antagonist, as well as by naloxone (Fig. 6A). The analgesia induced by exposure to the scent of the mainland male was also significantly, $F(2,23)=2.94$, $p<0.05$, reduced, though not completely blocked, by naloxone and the benzodiazepine agonist and antagonist.

In both the island and the mainland populations, the analgesic responses induced by peppermint were unaffected by either pre- or postexposure injections of diazepam, Ro 15-1788 and the vehicle, but were blocked, $F(4,48)=3.82$, $p<0.01$, by naloxone (Figs. 5B, 6B). Saline, the benzodiazepine vehicle and naloxone had no significant effects on the nociceptive responses of the control handled mice of either population (Fig. 4). Diazepam and Ro 15-1788, at the presently used doses did, however, have by themselves slight, but significant, $F(2,23)=2.78$, $p<0.05$, analgesic effects in both populations. There were no significant differences between the responses of the two populations to these doses of diazepam and Ro 15-1788.

DISCUSSION

Our results demonstrate that: 1) deer mice can distinguish and respond to isolated individuals from the same and different populations on the basis of olfactory cues, 2) there are marked differences between the analgesic responses of island and mainland populations of deer mice to the scent of an isolated, potentially threatening animal and 3) there are population differences in opioid and nonopioid, benzodiazepine sensitive, mediation of scent-induced analgesia. We show that the relative sensitivities to the scents of males from different populations, amplitudes of the scent-induced analgesia, as well as the sensitivity of the analgesia to benzodiazepine agonists and antagonist differs between these particular island and mainland populations of deer mice.

As we reported previously (21), exposure of males from the mainland population of deer mice, *P. m. artemisiae*, to the olfactory cues associated with an isolated conspecific, induced an analgesic response that was attenuated by peripheral administrations of either the benzodiazepine agonist or antagonist and was insensitive to blockade by the prototypic opiate antagonist naloxone. Exposure to the scent of an island male also induced an analgesic response. This latter, lower amplitude scent-induced analgesia, was however, blocked by naloxone and only partially reduced by the benzodiazepine manipulations. In addition, while

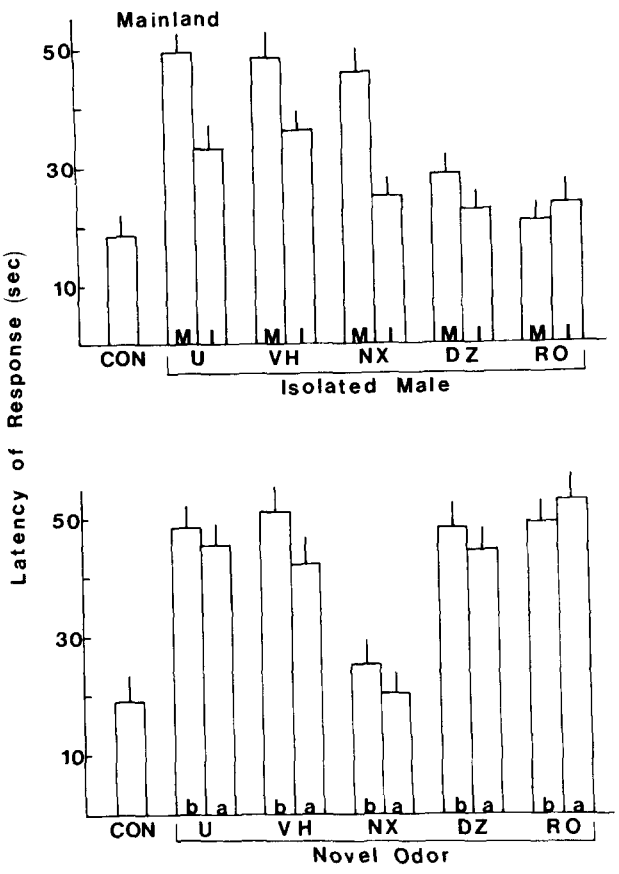

FIG. 5. (A–B) Effects of treatment with either naloxone (NX; 1.0 mg/kg); diazepam (DZ; 4.0 mg/kg); Ro 15-1788 (RO; 10 mg/kg); vehicle (VH; 10 ml/kg) or control handling without injection (U) on the thermal responses latencies of mainland deer mice, *P. m. artemisiae*, exposed to: (A) the soiled bedding of either an isolated mainland (M) or island (I) male for 30 min; (B) the novel odor of peppermint (30 min). The thermal response latencies of mice receiving only control handling (CON) are provided for comparison. Mice exposed to the odor of peppermint received treatments either directly before (b) or after (a) the exposures. In those injected beforehand, the response latencies were determined directly after exposure. In those individuals injected after exposure, thermal response latencies were measured 15 in later. N = 12, in all cases. Vertical lines denote a standard error of the mean.

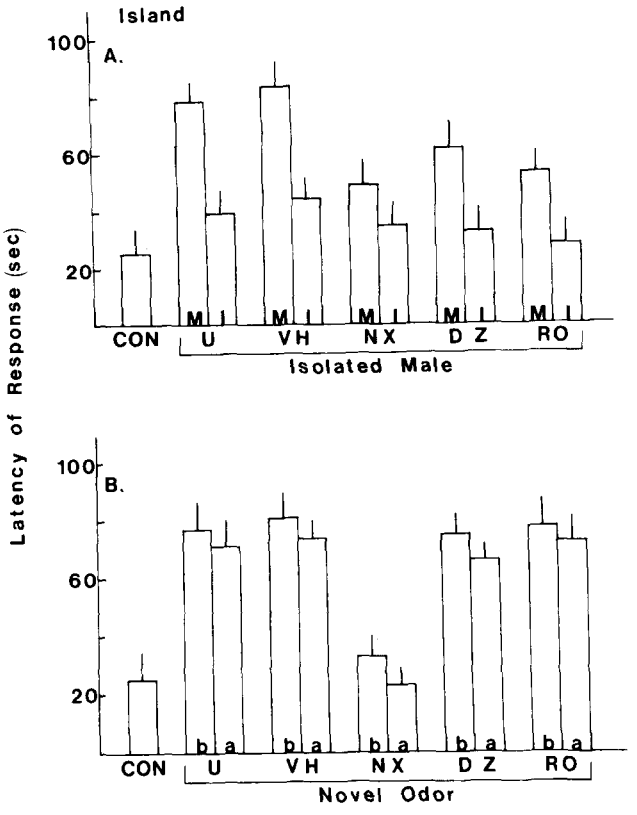

FIG. 6. (A–B) Effects of treatment with either naloxone (NX; 1.0 mg/kg); diazepam (DZ; 4.0 mg/kg); Ro 15-1788 (RO; 10 mg/kg); vehicle (VH; 10 ml/kg) or control handling without injection (U) on the thermal response latencies of deer mice, *P. m. angustus*, from an island exposed to: (A) the soiled bedding of either an isolated island (I) or mainland (M) male for 30 min; (B) the novel odor of peppermint (30 min). The thermal response latenices of mice receiving only control handling (CON) are provided for comparison. Mice exposed to the odor or peppermint received treatments either directly before (b) or after (a) the exposures. In those injected beforehand, the response latencies were determined directly after exposure. In those individuals injected after exposure, thermal response latencies were measured 15 min later. N = 12, in all cases. Vertical lines denote a standard error of the mean.

a one-minute exposure to the conspecific induced an immediate analgesic response, a similar exposure to the scent of an island male had no significant effect on the nociceptive responses of the mainland animal. Exposure of males from the island population of deer mice, *P. m. angustus*, for 30 min to the olfactory cues associated with an isolated island mouse elicited an analgesic response that was attenuated by naloxone and slightly reduced by the benzodiazepine manipulations. Exposure to the scent of a mainland male elicited a greater analgesic response that was blocked by naloxone and also only partially reduced by the benzodiazepine antagonist and agonist. A one-minute exposure to the scent of either a conspecific or a mainland animal also induced analgesic responses. However, in contrast to the immediate response observed in the mainland mice, scent-induced analgesia was evident in the island population only 15 min after the one-min exposure. Results of prior investigations have shown that island-mainland population differences in behavioral neuromodulation are consistent across populations (17, 19, 20). Thus, although only a single island and mainland subspecies was examined in the present study, it is likely that these differences in response are representative of the responses of other populations from small islands and larger mainland regions.

It was previously established that the benzodiazepine agonist and antagonist had similar inhibitory effects in mainland deer mice when administered either before or after exposure to the scent of another individual from the same population. This indicates that the central neurochemical mechanisms involved in processing the olfactory cues and eliciting an analgesic response, rather than the mechanisms involved in the perception of the scent of the conspecific, are affected by the benzodiazepine and opiate manipulations. This does not, however, completely exclude the possibility of some benzodiazepine and opioid mediated effects on perceptual mechanisms.

Neither exposure to the soiled bedding of a mixed sex pair of animals nor the presence of a clean substrate, had any significant effect on the nociceptive responses of the deer mice from either population. This indicates that the presence of clean bedding as

well as the scents of a male-female pair elicited minimal novelty or stress-related responses in the deer mice. It is likely that in the mixed sex bedding the scent of the female may have either masked or reduced any aversive elements associated with the scent of the different male. The odor of peppermint did, however, elicit a significant analgesia, which in both populations was blocked by either pre- or postexposure treatments with naloxone and unaffected by the benzodiazepine manipulations. This further indicates that the male scent-induced analgesia does not just arise from the presence of a novel or physically stressful odor, but rather, that it depends on the recognition of biologically relevant olfactory cues associated with the individually housed, aggressive, animals. This does not, however, preclude the possibility of the peppermint having a physically irritating effect on the deer mice.

There were also population differences in the peppermint-induced analgesia, the island mice displaying significantly greater analgesic responses than the mainland population. This confirms and extends previous findings of population differences in stress and novelty induced analgesia in deer mice (31,32).

Fear and 'anxiety' have been associated with alterations in the activity of benzodiazepine systems. It has been suggested the benzodiazepine-gamma amino butyric acid (GABA) receptor chloride ion complex is under tonic and acute regulation by the environment and has physiologically relevant roles in mediating responses to stressful stimuli (41). Results of biochemical studies have shown that acute stress can apparently, rapidly and reversibly alter benzodiazepine and GABA binding, modulate the functioning of chloride channels that are coupled to the GABA complex and increase the number of benzodiazepine binding sites (15,41). The inhibitory effects of both the benzodiazepine agonist and antagonist on the scent-induced analgesia may, in part, arise from the partial agonist properties of the antagonist, Ro 15-1788 (4), and/or differential effects on multiple benzodiazepine binding sites.

Results of investigations with laboratory mice and rats have revealed strain differences in the apparent activity of benzodiazepine systems and sensitivity to benzodiazepine agonists and antagonists (2, 9, 10, 24, 27, 36). There are also indications of possible genetic differences in various neurochemical aspects of the regulation of the activity of the benzodiazepine complex (2). Thus, the differential expression and/or activation of benzodiazepine systems may contribute to the behavioral differences between island and mainland populations of deer mice. This does not, however, preclude the possibility of either direct or indirect effects of other neurochemical systems that are involved in the modulation of the scent-induced behaviour. In particular, specific steroid metabolites of progesterone and deoxycorticosterone that have been shown to affect the functioning of the benzodiazepine-GABA-chloride channel complex are implicated in the mediation of analgesic and other behavioral responses to stressful situations (7,18). Moreover, recent evidence has been presented to suggest that serotoninergic (5-HT_{1A}) binding sites rather than benzodiazepine recognition sites are involved in the mediation of nonopioid defeat-induced analgesia in DBA/2 mice (33,34). How these sites and mechanisms may relate to either scent-induced analgesia or population differences in responses to male odors is under consideration.

ACKNOWLEDGEMENTS

We thank Dr. J. Millar for providing the deer mice. This research was supported by a Natural Sciences and Engineering Research Council of Canada operating grant to M.K. (D034A1).

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