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Sex and Genotype Determine the Selective Activation of Neurochemically-Distinct Mechanisms of Swim Stress-Induced Analgesia

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MOGIL, J. S. and J. K. BELKNAP. *Sex and genotype determine the selective activation of neurochemically-distinct mechanisms of swim stress-induced analgesia.* PHARMACOL BIOCHEM BEHAV. **56**(1) 61–66, 1997. — A growing literature documents the important influence of organismic factors such as sex and genotype on pain sensitivity and pain modulation. We recently determined that 3-min forced swims in 15°C water produce non-opioid (i.e., naloxone-insensitive) analgesia in outbred Swiss–Webster mice of both sexes; this form of stress-induced analgesia (SIA) is significantly attenuated by the *N*-methyl-D-aspartate (NMDA) antagonist, dizocilpine (MK-801) in males, but not females. A pilot study designed to confirm the non-opioid and (in male mice) NMDAergic nature of 15°C swim SIA in the C57BL/6J and DBA/2J inbred strains used widely in gene mapping was conducted, using the hot-plate (54°C) assay of nociception. In female mice of both strains, 15°C swim SIA was insensitive to antagonism by either naloxone (10 mg/kg, IP) or dizocilpine (0.1 mg/kg, IP). In male C57BL/6J mice, the observed SIA was naloxone-insensitive, but was attenuated by dizocilpine. This pattern of results is virtually identical to that obtained using Swiss–Webster mice in this and previous studies. However, male DBA/2J mice displayed SIA that was significantly attenuated by naloxone, but insensitive to dizocilpine antagonism. These findings support the hypothesis that genetic factors and sex, in addition to stressor parameters, can determine the selective recruitment of alternative central mechanisms of pain inhibition. **Copyright © 1997 Elsevier Science Inc.**

Genetics Sex differences Non-opioid DBA/2 mice C57BL/6 mice

TWO DECADES of research into the phenomenon of stress-induced analgesia (SIA), whereby environmental stressors activate endogenous mechanisms of pain inhibition, has demonstrated unequivocally that the mammalian brain possesses multiple pain inhibitory systems [e.g., (18)]. These separate circuitries have been dissociated based on neurochemistry, neuroanatomy, and their selective recruitment by different stressors or stress parameters. The earliest dissociation of SIA mechanisms was into "opioid" and "non-opioid" forms, based on their sensitivity or refractoriness to systemic antagonism by the prototypic opiate receptor antagonists, naloxone and naltrexone (1,18). More recently, evidence has accumulated that these two broad classes of SIA can be further subdivided into neural versus humoral forms, unconditioned versus conditioned forms, and spinally- versus supraspinally-mediated forms [see (36)].

A number of detailed parametric investigations have defined specific stress parameters (of footshock, tailshock, or forced swimming) producing alternate neurochemical forms of SIA (7,18,20,32,33). In our hands, 3-min forced swimming in warm (30–38°C) and cold (10–20°C) water produces opioid (i.e., naloxone-reversible) and non-opioid (i.e., naloxone-insensitive) SIA, respectively (21, 24, 28). Furthermore, non-opioid SIA can be obtained from warm-water swims of sufficiently long (7-min) duration, and opioid SIA can be obtained from cold-water swims of sufficiently short (45-s) duration (24). Thus, we have proposed that in the mouse, as in the rat (7,32), forced swims of mild severity (warm water and/or short-duration) selectively recruit opioid analgesic mechanisms whereas more severe swims (cold water and/or long-duration) recruit non-opioid analgesic mechanisms.

It is clear, however, that parametric considerations do not fully explain the complex relationship between environmental stress and pain inhibition. SIA magnitude is known to

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be modulated by a number of organismic factors, including gender, estrus phase, age, and developmental experience [see (6, 12) for reviews]. Qualitative sex differences in SIA physiology have been noted as well. For instance, we have recently determined that the non-opioid SIA resulting from 3-min swims in 15°C water is antagonized by the *N*-methyl-D-aspartate (NMDA) receptor antagonist, dizocilpine (MK-801; 0.075 mg/kg, IP), in male but not female mice (25). Female mice exhibit male-like, dizocilpine-sensitive SIA upon ovariectomy, and an estrogen-replacement regimen reinstates their insensitivity. Importantly, although 3-min, 15°C swims produce SIA in female mice that is entirely non-opioid and non-NMDAergic, the SIA observed is equipotent to that of males. We concluded, therefore, that female mice must possess a sex-specific, estrogen-dependent SIA mechanism of unknown neurochemical identity (25).

Genetic factors also appear to play an important role in the mediation of pain inhibition [see (4, 26) for reviews]. Large differences between inbred mouse strains have been documented in pain-relevant traits, and mice selectively bred for high and low magnitudes of swim SIA (HA and LA lines) diverged significantly from controls in only a single generation (27). In addition to genetically-determined SIA magnitude differences, one piece of evidence suggests that genetic factors may also determine the selective recruitment of opioid versus non-opioid SIA mechanisms by footshock (35). At present, however, the identity of genes relevant to SIA remain elusive.

The present study was intended to confirm the non-opioid and (presumably in male mice only) NMDAergic nature of 15°C swim SIA in two common inbred strains, C57BL/6J (B6) and DBA/2J (D2). These strains are ancestral to the BXD/Ty recombinant inbred (RI) strain set (31) we are using to map quantitative trait loci (QTLs; i.e., chromosomal loci associated with quantitative traits) (11) underlying 15°C swim SIA. However, data obtained presently from B6 and D2 mice of both sexes reveal that the neurochemical nature of 15°C swim SIA appears to be determined by *both* genotype and sex. Since slightly different testing parameters (e.g., hot-plate temperature, dizocilpine dose) were used presently as compared with previous efforts using Swiss-Webster (SW) mice (21, 25), we also retested SW mice in this study.

METHOD

Naive, adult (8–12 wk old) SW ($N = 60$), B6 ($N = 56$), and D2 ($N = 52$) mice of both sexes were used. All mice were bred at the VA Medical Center (Portland, OR) from breeders obtained from Simonsen (Gilroy, CA; SW mice) and The Jackson Laboratory (Bar Harbor, ME; B6 and D2 mice). Animals were housed with their same-sex littermates (2–5 mice per cage) in a light/dark cycle of 12:12 h (lights on at 07:00 h), and had ad lib access to food (Purina chow) and tap water.

All testing proceeded near the midpoint of the animals light/dark cycle (13:00–16:00 h), in order to minimize circadian effects on analgesic sensitivity (16). B6 and D2 mice were tested concurrently, in order to control for testing day variability. SW mice were tested separately, but using identical protocols. Mice of all three strains (and both sexes) were randomly assigned to one of three drug pretreatment conditions: saline, naloxone (10 mg/kg; Sigma, St. Louis, MO), or dizocilpine (0.1 mg/kg; RBI, Natick, MA). All drugs were administered intraperitoneally (10 ml/kg injection volume) 30 min prior to initial nociceptive testing. These doses of naloxone and dizocilpine were chosen for their maximal antagonistic effects on opioid and non-opioid SIA, respectively, as defined by previous investigations using SW mice (15, 21, 24, 25, 29) and pilot data using B6 and D2 mice. In addition, the dizocilpine dose was chosen to be selective to non-opioid SIA, since higher doses (0.25 mg/kg) have been shown to reverse morphine analgesia and opioid-mediated restraint analgesia in deer mice (19).

Nociceptive sensitivity was assessed using the hot-plate assay (9), a test of latency to respond to an acute, thermal noxious stimulus. The hot-plate (Thermolyne Dri-Bath) temperature was maintained at 54.0 ± 0.2°C. Mice were placed on the metal surface of the plate, constrained by 15-cm high Plexiglas walls to an area 10 × 10 cm. Latency to respond to the heat stimulus was measured to the nearest 0.1 s by an experienced observer blind to drug condition. Mice remained on the plate until they performed one of the following behaviors regarded as indicative of nociception: hindpaw lift, lick or shake/flutter. In the absence of any of these responses after 60 s, the mice were removed from the hot plate and a cut-off latency of 60 s was recorded.

Immediately after assessment of baseline hot-plate latency, all mice were subjected to 3-min forced swimming in 15°C water. The swims were carried out in a cylindrical plastic container 28 cm in diameter and 44 cm in height. The water level ranged from 30–35 cm high, so that escape was impossible. Water temperature was monitored carefully by an experimenter, and maintained at 15 ± 1°C by the addition of ice. Upon completion of the 3-min swim, mice were towel-dried and placed in a paper towel-lined enclosure for 2 min to dry. After this drying-off period, animals were retested on the hot plate.

Analgesia was defined as a significant pre-swim versus post-swim repeated measure. For purposes of group comparisons and illustration, analgesia was expressed as percentage of the maximum possible effect (%MPE), as calculated by the following formula:

$$\%\text{MPE} = \frac{(\text{post-swim latency} - \text{baseline latency})}{(\text{cut-off latency} - \text{baseline latency})} \times 100$$

The use of %MPEs take into account the cut-off latency and individual baseline latencies, so that these will not bias the quantification of analgesia. Furthermore, this transformation normalizes the distribution of the data so parametric statistics can be used. Baseline latencies (in s) and analgesia scores (expressed as %MPE) were analyzed by ANOVA, followed where appropriate by the Tukey post-hoc test. The criterion alpha level of significance was chosen to be $p < .05$.

RESULTS

Since B6 and D2 mice were run concurrently, but SW mice were tested alone, we analyzed data from SW mice separately from those of B6/D2 mice. For both data sets, ANOVA revealed a significant main effect of drug on baseline hot-plate latency. Post-hoc analyses showed a significant reduction of baseline latencies in all strains by naloxone; found to be significant in male, but not female mice (Table 1). We have observed this effect of naloxone before (21, 24, 25), and believe it to represent the antagonism of a mild, opioid-mediated form of SIA related to the injection and/or testing process. Dizocilpine had no significant effect on baseline nociception in any group. There were no significant sex differences in baseline latencies of saline-treated mice of any strain.

Repeated measures ANOVA revealed the existence of significant analgesia in all experimental groups. A two-way

TABLE 1

EFFECT OF NALOXONE (NAL) AND DIZOCILPINE (DIZ) ON THERMAL NOCICEPTIVE SENSITIVITY OF SW, B6, AND D2 MICE OF BOTH SEXES IMMEDIATELY BEFORE, AND 2-MIN AFTER A 3-MIN SWIM IN 15°C WATER

				Hot-Plate Latency (s)†	
Sex	Strain	Drug*	*N*	Pre-Swim	Post-Swim
Male	SW	Saline	10	16.2 ± 0.7	45.7 ± 4.9
		NAL	10	12.3 ± 0.4‡	48.0 ± 4.3
		DIZ	10	16.3 ± 1.7	26.8 ± 4.4§
	B6	Saline	9	22.3 ± 2.5	57.3 ± 2.2
		NAL	8	14.2 ± 1.8‡	55.4 ± 3.6
		DIZ	11	19.6 ± 2.5	40.3 ± 3.8§
	D2	Saline	10	22.6 ± 1.0	55.2 ± 4.2
		NAL	10	15.1 ± 2.2‡	31.0 ± 6.0§
		DIZ	7	19.3 ± 3.7	47.7 ± 4.9
Female	SW	Saline	10	15.5 ± 0.8	49.8 ± 3.4
		NAL	10	13.4 ± 0.6	52.7 ± 2.7
		DIZ	10	14.0 ± 0.6	49.4 ± 4.4
	B6	Saline	9	21.1 ± 2.3	55.6 ± 1.8
		NAL	9	16.4 ± 1.3	54.3 ± 4.6
		DIZ	10	20.1 ± 2.3	53.1 ± 4.6
	D2	Saline	8	21.1 ± 3.8	54.8 ± 5.2
		NAL	9	16.3 ± 0.9	51.6 ± 5.0
		DIZ	8	17.1 ± 1.6	43.6 ± 7.1

*All drugs were injected intraperitoneally in a volume of 10 ml/kg, 30 min prior to assessment of baseline nociceptive sensitivity. NAL dose, 10 mg/kg. DIZ dose, 0.1 mg/kg.

†Values represent means ± SE. All post-swim means are significantly higher than corresponding pre-swim means.

‡Significantly different than corresponding saline mean, $p < .05$.

§Significantly different than corresponding saline mean and corresponding female mean, $p < .05$.

ANOVA (sex × drug) performed on SW %MPE data revealed significant main effects of sex [$F(1, 54) = 9.83$] and drug [$F(2, 54) = 5.22$], and a significant sex × drug interaction [$F(2, 54) = 3.68$]. A simple main effect of drug was observed in male mice only [$F(2, 27) = 6.97$]. As previously observed with slightly different testing parameters (24), naloxone was ineffective in reducing 15°C swim SIA in both sexes, and dizocilpine significantly antagonized this SIA in male, but not female SW mice (Fig. 1). A three-way ANOVA (strain × sex × drug) performed on B6/D2 %MPE data revealed a significant main effect of drug [$F(2, 96) = 4.51$] and a significant strain × sex × drug interaction [$F(2, 96) = 4.21$]. SIA in female mice of both strains was unaffected by naloxone or dizocilpine, and the SIA exhibited by male B6 mice was significantly attenuated by dizocilpine only. Unexpectedly, the SIA displayed by male D2 mice was unaffected by dizocilpine, but significantly attenuated by naloxone (Fig. 2). The magnitude of SIA displayed by saline-treated mice of all groups was found to be equivalent.

It is conceivable that the different strains and sexes tested presently merely have altered dose-response curves to naloxone and/or dizocilpine for pharmacokinetic or other reasons. To evaluate this possibility, we tested lower doses of naloxone (0.1 and 1 mg/kg) in female mice of all three strains and male B6 mice, and a higher dose of dizocilpine (0.25 mg/kg) in female mice of all three strains and male D2 mice. Testing doses of naloxone higher than 10 mg/kg was unnecessary because opiate receptors are already saturated at this dose (8),

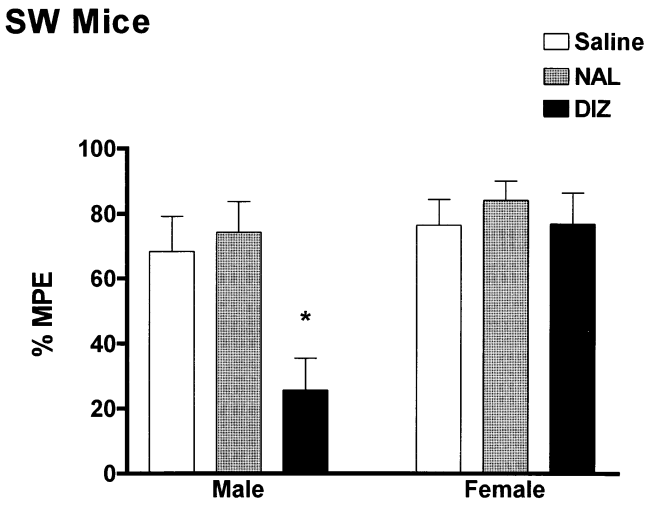

FIG. 1. Effect of naloxone (NAL; 10 mg/kg, IP) and dizocilpine (DIZ; 0.1 mg/kg, IP) on swim SIA in male and female SW mice. All mice were tested for nociceptive sensitivity on the hot plate (54°C) immediately before and 2 min after a 3-min forced swim in 15°C water. Analgesia is represented as percentage of maximum possible effect (%MPE). Bars represent means ± SE. *$p < .05$ compared to saline.

and testing doses of dizocilpine higher than 0.25 mg/kg was precluded by increasing motoric impairment. Supporting our previous findings in SW mice, these additional doses were similarly ineffective in producing antagonism of 15°C swim SIA (data not shown).

DISCUSSION

The present data replicate and extend our previous findings using SW mice (25), that female mice display non-opioid 15°C swim SIA that is insensitive to antagonism by dizocilpine, but is nonetheless equipotent to that of males. The sex difference persists using a slightly higher dizocilpine dose (0.1 mg/kg vs. 0.075 mg/kg), a lower hot-plate temperature (54°C vs. 56°C), and a different experimental design (between- vs. within-subject) in the present study. Subsequent to our initial demonstrations (21, 22, 25), the antagonism of non-opioid swim SIA by dizocilpine has been observed in male rats (5) and non-SW mice (14,15). Furthermore, recent studies have elaborated on this finding, showing the sex difference in non-opioid swim SIA mediation to be dependent on neonatal testosterone exposure (29), age (Sternberg et al., in preparation), and breeding status (15). Intriguingly, one report demonstrates that swim stress increases [^{3}H]-dizocilpine binding in forebrain synaptosomal membranes of male mice, but has no effect on binding in females (2). We now report that B6 mice also exhibit a sex difference in the ability of dizocilpine to antagonize 15°C swim SIA. The large database of neurobiological information already collected in this commonly-used inbred strain [see (13)] should facilitate the further exploration of this phenomenon.

We believe the present findings also establish in mice what Urca and colleagues (35) have proposed based on their data from different rat strains: the predominance of opioid versus non-opioid SIA can be determined by genetic factors as well as stress parameters. In their study, seven strains of rats (two lines of Wistar, three lines of Sprague–Dawley, Wistar–Kyoto, and Sabra) were tested for SIA following 30-min intermittent footshock (3 mA; 1 s on, 5 s off), shown by Lewis et al. (18)

to be naloxone-reversible. Only in the Sabra strain and one line of Sprague–Dawley was significant attenuation of this SIA by naloxone observed. The naloxone-insensitive strains *did* have the capacity to exhibit opioid analgesia, since electrical stimulation of or morphine microinjection into the ventral periaqueductal gray of these animals produced potent, naloxone-reversible analgesia. The present data can be considered complementary to those of Urca and colleagues (35), since D2 mice exhibit opioid SIA from stress parameters that are expected to produce non-opioid SIA.

It is conceivable that the sex and genotype differences observed presently with respect to dizocilpine antagonism of swim SIA are secondary to motoric effects of this drug. NMDA channel blockers such as dizocilpine and phencyclidine can produce locomotor activating effects in rodents, and at higher doses a psychotomimetic-like motor syndrome featuring head weaving, body rolling, stereotypy and ataxia (34). Locomotion is generally regarded as a competing response on the hot-plate test relative to nociceptive behaviors such as paw-lick/shake (10). However, we feel that it is unlikely that strain differences in dizocilpine hyperlocomotion underlie the present observations for a number of reasons. First, we have previously assessed locomotor responses of B6 and D2 mice to dizocilpine; only doses $\geq$0.25 mg/kg produce significant activation, and even at these doses the activation is *not* genotype-dependent (3). Second, we are unaware of any demonstrations of sex differences in dizocilpine-stimulated locomotion. Finally, we have replicated the sex difference in the reflexive tail-withdrawal assay, in which the subject is restrained and only gross motoric abnormalities can affect the nocifensive response (unpublished data).

The present data may have important implications for the characterization of alternative pain inhibitory mechanisms. B6 and D2 mice are among the least related of inbred strains in common use (30), and not surprisingly, a wide variety of differences between these strains have been documented [see (13)]. They are especially divergent with respect to opioid-mediated phenomena [see (4, 26)]; for instance, D2 mice display morphine hot-plate analgesic ED_{50}s that are more than 3-fold lower than those of B6 mice (23). Because of their genetic dissimilarity, these strains have been employed as the progenitors of the 26-strain BXD/Ty RI set (31), used widely in murine gene mapping efforts. We have already studied 15°C swim SIA in both sexes of 24 BXD strains, in the first of a two-phase QTL mapping approach (11). This trait was found to be moderately heritable (h^2 = .32) even though B6 and D2 mice exhibit 15°C swim SIA of equivalent magnitude, indicating the existence of several polygenes with canceling effects in the parental strains. A number of putative QTL regions have been identified for males (manuscript in preparation), but the present findings complicate the interpretation of these data. Indeed, we can no longer claim that these QTLs underlie non-opioid SIA magnitude, since in D2 mice (and presumably, therefore, in a proportion of the BXD strains) the SIA is at least partially opioid. Despite the interpretational difficulties these data impose, they do point to interesting new avenues of investigation. A comparison of the BXD strain distribution pattern of 15°C SIA in the presence versus absence of a high dose of naloxone should identify "opioid" and "non-opioid" BXD strains. This approach would allow the mapping of QTLs underlying the recruitment of different mechanisms of analgesia from the same stressor.

Since female mice of both the B6 and D2 strains display no opioid SIA after 15°C swims, QTLs obtained from analysis of female BXD and (B6xD2)F_2 mice can be unambiguously

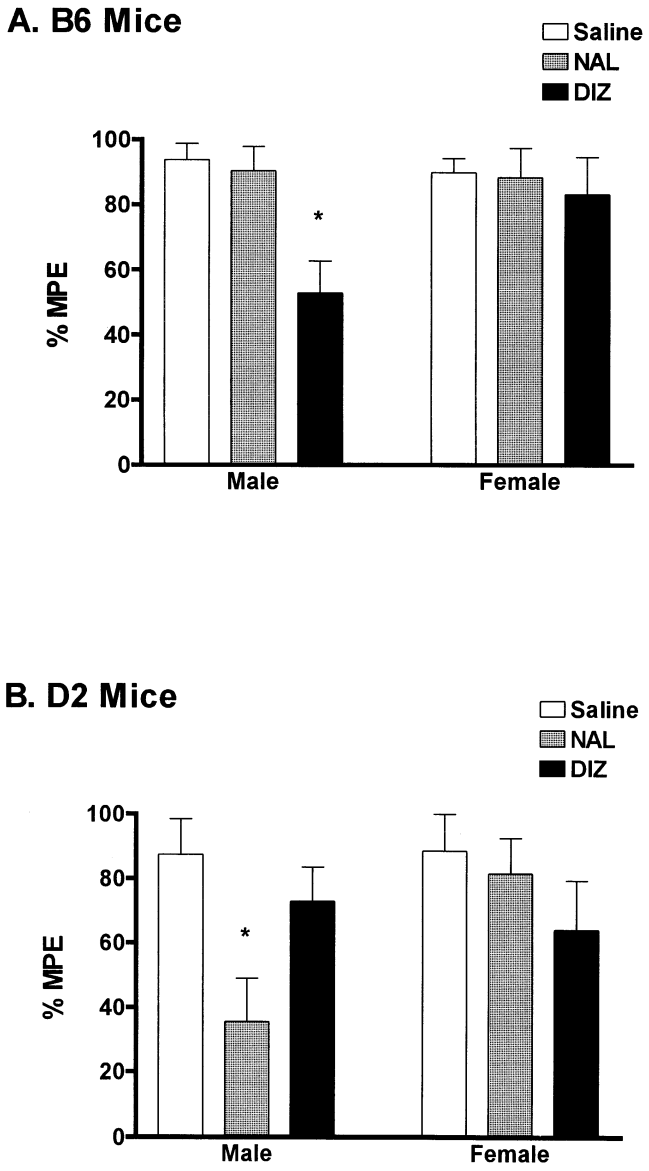

FIG 2. Effect of naloxone (NAL; 10 mg/kg, IP) and dizocilpine (DIZ; 0.1 mg/kg, IP) on swim SIA in B6 (A), and D2 (B) mice of both sexes. All mice were tested for nociceptive sensitivity on the hot plate (54°C) immediately before and 2 min after a 3-min forced swim in 15°C water. Analgesia is represented as percentage of maximum possible effect (%MPE). Bars represent means ± SE. *$p < .05$ compared to saline.

considered to underlie non-opioid SIA in this sex. The neurochemical identity of non-opioid swim SIA in females is at present completely undefined. Given the myriad neuromodulators purported to affect non-opioid analgesia (e.g., glutamate, serotonin, acetylcholine, norepinephrine, histamine, dopamine, simultaneous activation of multiple opiate receptors) [e.g., (17, 21, 37)], determining the neurochemistry of female-specific non-opioid swim SIA by conventional pharmacological techniques would be a daunting task. We believe that QTL mapping of 15°C swim SIA might simplify this endeavor. Once QTLs are identified for this phenotype, one can consult recent genetic linkage maps to assess whether any neurochemically-

relevant genes have already been mapped to the same location. Candidate genes so identified can then be subjected to confirmation by pharmacological and/or molecular techniques. Our mapping data thus far do, in fact, suggest a number of female-specific QTLs associated with both baseline nociceptive sensitivity and 15°C swim SIA (manuscript in preparation), supporting in a novel manner the contention that females may employ sex-specific mechanisms of pain modulation.

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REFERENCES

1. Akil, H.; Madden, J.; Patrick, R. L.; Barchas, J. D. Stress-induced increase in endogenous opiate peptides; Concurrent analgesia and its partial reversal by naloxone. In: Kosterlitz, H. W. ed. Opiates and endogenous opioid peptides. Amsterdam: Elsevier/North Holland; 1976:63–70.
2. Akinci, M. K.; Johnston, G. A. R. Sex differences in acute swim stress-induced changes in the binding of MK-801 to the NMDA subclass of glutamate receptors in mouse forebrain. J. Neurochem. 61:2290–2293; 1993.
3. Angeli-Gade, S.; Phillips, T. J.; Belknap, J. K. Locomotor responses of C57BL/6J and DBA/2J inbred mice to MK-801. Alcohol: Clin. Exp. Res. 16:309; 1992.
4. Belknap, J. K.; O'Toole, L. A. Studies of genetic differences in response to opioid drugs. In: Harris, R. A.; Crabbe, J. C. eds. The genetic basis of alcohol and drug actions. New York: Plenum Press; 1991:225–252.
5. Ben-Eliyahu, S.; Page, G. G.; Marek, P.; Kest, B.; Taylor, A. N.; Liebeskind, J. C. The NMDA receptor antagonist MK-801 blocks non-opioid stress induced analgesia and decreases tumor metastasis in the rat. Proc. West. Pharmacol. Soc. 36:293–298; 1993.
6. Bodnar, R. J.; Romero, M.-T.; Kramer, E. Organismic variables and pain inhibition: roles of gender and aging. Brain Res. Bull. 21:947–953; 1988.
7. Bodnar, R. J.; Sikorszky, V. Naloxone and cold-water swim analgesia: parametric considerations and individual differences. Learn. Motivation 14:223–237; 1983.
8. Dykstra, L. A.; Bertalmio, A. J.; Woods, J. H. Discriminative and analgesic effects of mu and kappa opioids. In vivo pA_2 analysis. In: Colpaert, F.; Balster, R. eds. Psychopharmacology Series 4: Transduction Mechanisms of Drug Stimuli. New York: Springer–Verlag; 1988:107–121.
9. Eddy, N. B.; Leimbach, D. Synthetic Analgesics II. Diethienylbutenyl- and dithienylbutylamines. J. Pharmacol. Exp. Ther. 107:385–393; 1953.
10. Espejo, E. F.; Mir, D. Structure of the rat's behaviour in the hot plate test. Behav. Brain Res. 56:171–176; 1993.
11. Gora-Maslak, G.; McClearn, G. E.; Crabbe, J. C.; Phillips, T. J.; Belknap, J. K.; Plomin, R. Use of recombinant inbred strains to identify quantitative trait loci in psychopharmacology. Psychopharmacology 104:413–424; 1991.
12. Hamm, R. J.; Knisely, J. S. Developmental aspects of nociception. Brain Res. Bull. 21:933–946; 1988.
13. Ingram, D. K.; Corfman, T. P. An overview of neurobiological comparisons in mouse strains. Neurosci. Biobehav. Rev. 4:421–434, 1980.
14. Kamei, J.; Kawashima, N.; Ohhashi, Y.; Kasuya, Y. Effects of diabetes on stress-induced analgesia in mice. Brain Res. 580:180–184; 1992.
15. Kavaliers, M.; Galea, L. A. M. Sex differences in the expression and antagonism of swim stress-induced analgesia in deer mice vary with the breeding season. Pain 63:327–334; 1996.
16. Kavaliers, M.; Hirst, M. Daily rhythms of analgesia in mice: Effects of age and photoperiod. Brain Res. 279:387–393; 1983.
17. Kiefel, J. M.; Bodnar, R. J. Roles of gender and gonadectomy in pilocarpine and clonidine analgesia in rats. Pharmacol. Biochem. Behav. 41:153–158; 1991.
18. Lewis, J. W.; Cannon, J. T.; Liebeskind, J. C. Opioid and nonopioid mechanisms of stress analgesia. Science 208:623–625; 1980.
19. Lipa, S. M.; Kavaliers, M. Sex differences in the inhibitory effects of the NMDA antagonist, MK-801, on morphine and stress-induced analgesia. Brain Res. Bull. 24:627–630; 1990.
20. Maier, S. F. Determinants of the nature of environmentally induced analgesia. Behav. Neurosci. 103:131–143; 1989.
21. Marek, P.; Mogil, J. S.; Sternberg, W. F.; Panocka, I.; Liebeskind, J. C. *N*-methyl-D-aspartic acid (NMDA) receptor antagonist MK-801 blocks non-opioid stress-induced analgesia. II. Comparison across three swim stress paradigms in selectively bred mice. Brain Res. 578;197–203; 1992.
22. Marek, P.; Page, G. G.; Ben-Eliyahu, S.; Liebeskind, J. C. NMDA receptor antagonist MK-801 blocks non-opioid stress-induced analgesia. I. Comparison of opiate receptor-deficient and opiate receptor-rich strains of mice. Brain Res. 551:293–296; 1991.
23. Mogil, J. S.; Kest, B.; Sadowski, B.; Belknap, J. K. Differential genetic mediation of sensitivity to morphine in genetic models of opiate antinociception: influence of nociceptive assay. J. Pharmacol. Exp. Ther. 276:532–544; 1996.
24. Mogil, J. S.; Sternberg, W. F.; Balian, H.; Liebeskind, J. C.; Sadowski, B. Opioid and non-opioid swim stress-induced analgesia: a parametric analysis in mice. Physiol. Behav. 59:123–132; 1996.
25. Mogil, J. S.; Sternberg, W. F.; Kest, B.; Marek, P.; Liebeskind, J. C. Sex differences in the antagonism of swim stress-induced analgesia: effects of gonadectomy and estrogen replacement. Pain 253:17–25; 1993.
26. Mogil, J. S.; Sternberg, W. F.; Marek, P.; Sadowski, B.; Belknap, J. K.; Liebeskind, J. C. The genetics of pain and pain inhibition. Proc. Natl. Acad. Sci. USA 93:3048–3055; 1996.
27. Panocka, I.; Marek, P.; Sadowski, B. Inheritance of stress-induced analgesia in mice. Selective breeding study. Brain Res. 397:152–155; 1986.
28. Rubinstein, M.; Mogil, J. S.; Japon, M.; Chan, E. C.; Allen, R. G.; Low, M. J. Absence of opioid stress-induced analgesia in mice lacking β-endorphin by site-directed mutagenesis. Proc. Natl. Acad. Sci. USA 93:3995–4000; 1996.
29. Sternberg, W. F.; Mogil, J. S.; Kest, B.; Page, G. G.; Leong, Y.; Yam, V.; Liebeskind, J. C. Neonatal testosterone exposure influences neurochemistry of swim stress-induced analgesia in adult mice. Pain 63:321–326; 1996.
30. Taylor, B. A. Genetic relationships between inbred strains of mice. J. Hered. 63:83–86; 1972.
31. Taylor, B. A. Recombinant-inbred strains: use in gene mapping. In: Morse, H. C., III, ed. Origin of inbred mice. New York: Academic Press; 1978:423–428.
32. Terman, G. W.; Morgan, M. J.; Liebeskind, J. C. Opioid and nonopioid stress analgesia from cold water swim: importance of stress severity. Brain Res. 372:167–171; 1986.
33. Tierney, G.; Carmody, J. J.; Jamieson, D. Stress analgesia: the opioid analgesia of long swims suppresses the non-opioid analgesia induced by short swims in mice. Pain 46:89–95; 1991.
34. Tricklebank, M. D.; Singh, L.; Oles, R. J.; Preston, C.; Iversen, S. D. The behavioral effects of MK-801: a comparison with antagonists acting non-competitively and competitively at the NMDA receptor. Eur. J. Pharmacol. 167:127–135; 1989.

35. Urca, G.; Segev, S.; Sarne, Y. Footshock-induced analgesia: its opioid nature depends on the strain of rat. Brain Res. 329:109–116; 1985.
36. Watkins, L. R.; Mayer, D. J. Multiple endogenous opiate and non-opiate analgesia systems: evidence of their existence and clinical implications. Ann. N. Y. Acad. Sci. 467:273–299; 1986.
37. Watkins, L. R.; Wiertelak, E. P.; Grisel, J. E.; Silbert, L. H.; Maier, S. F. Parallel activation of multiple spinal opiate systems appears to mediate "non-opiate" stress-induced analgesias. Brain Res. 594:99–108; 1992.