

Strain and Model Differences in Behavioral Outcomes after Spinal Cord Injury in Rat

CHARLES D. MILLS, BRYAN C. HAINS, KATHIA M. JOHNSON,
and CLAIRE E. HULSEBOSCH

ABSTRACT

Spinal cord injury (SCI) results in loss of function below the level of injury and the development of chronic central pain (CCP) syndromes. Since different strains may develop and express chronic pain behaviors differently, we evaluated behavioral outcomes (locomotor recovery and the development of mechanical and thermal allodynia) in three commonly used strains of rats (Long-Evans, Wistar, and Sprague-Dawley) using two models of SCI. The two models examined were contusion at T10 (NYU impactor, 12.5 mm height) and the T13 hemisection. Mechanical stimulation (von Frey filaments) revealed significantly lower baseline responses for Long-Evans rats and significantly higher baseline paw withdrawal latencies to thermal stimulation for Wistar rats compared to the other strains. Following contusion SCI, Long-Evans rats had the highest percentage of animals that developed mechanical allodynia (73%), while Sprague-Dawley rats had the highest percentages (75%) following hemisection SCI. Interestingly, the Sprague-Dawley rats had the highest percentage (87%) to develop thermal allodynia following contusion SCI, while 100% of both Long-Evans and Sprague Dawley rats developed thermal allodynia in the hemisection model. Locomotor recovery after SCI was similar for each model in that Long-Evans rats recovered slower and to a lesser extent than the other strains. In each model, Sprague-Dawley rats recovered faster and achieved greater function. Overall, the hemisection model produced a larger percentage of animals that developed CCP and had greater responses to mechanical stimulation. Thus, it appears that strain selection has a greater impact on locomotor recovery and model selection has a greater impact on the development of CCP following SCI. Furthermore, these results suggest that genetic factors may play a role in recovery following SCI.

Key words: chronic central pain; contusion; hemisection; spinal cord injury; strain

INTRODUCTION

SPINAL CORD INJURY (SCI) is a devastating event that may result in a loss of function below the level of lesion and the development of chronic central pain (CCP) syndromes (Balazy, 1992; Beric et al., 1988; Boivie, 1984; Davidoff and Roth, 1991; Davidoff et al., 1987; Jack and Lloyd, 1983; Loubser and Donovan, 1996;

Nogues, 1987; Pagni, 1989; Richards et al., 1980; Rintala et al., 1998; Schliep, 1978; White, 1966). The percentage of patients with CCP may be as high as 75% (Christensen and Hulsebosch, 1997). The development of CCP greatly affects the quality of life, often resulting in depression and suicide (Cairns et al., 1996; Lundqvist et al., 1991; Segatore, 1994). Unfortunately, CCP seems to increase with time after injury and may be refractory to

treatment (Richards et al., 1980; Rintala et al., 1998; Yezierski, 2000).

There are several models that are used to study CCP and SCI (Ramer et al., 2000; Vierck, 1991; Vierck et al., 2000). The development of pain syndromes in experimental models is influenced not only by differences in the neurotrauma model employed, but also by environmental factors (e.g., maternal-fostering vs. cross-fostering), sex, age, diet, and genetic differences (DeLeo and Rutkowski, 2000; Mogil, 1999; Mogil et al., 1999a,b, 2000; Shir et al., 1998; Sudakov et al., 1996; Yoon et al., 1999).

Of particular interest is the genetic predisposition (or lack thereof) for the development of pain syndromes. When translating results from experimental animals to humans, it must be kept in mind that the patient population is genetically heterogeneous. While the use of inbred strains in experimentation is certainly important, outbred strains may more closely resemble the patient population. Recently, it has been reported that outbred rat strains were more responsive to sciatic nerve ligation than inbred strains (Lovell et al., 2000). One possible explanation is that there may be strain-specific neurochemical and morphological rearrangements in the spinal cord (Lovell et al., 2000). Outbred strains also demonstrate differences in the antinociceptive effect of nitrous oxide compared to inbred strains (Fender et al., 2000). Genes encoding for proteins and enzymes that metabolize anesthetic and analgesic agents, which ultimately influence pain receptors and pain-related behaviors, may differ between individuals (Nebert and Weber, 1990). While some "pain genes" have been identified, variation in pain-related responses is likely due to interactions of several genes acting in concert with the environment (Mogil, 1999).

Two models of CCP induced by SCI currently being used in our laboratory are the contusion and hemisection models (Christensen et al., 1996; Hains et al., 2000; Hulsebosch et al., 2000; Mills et al., 2001a). The present study was undertaken to examine the model and strain dependences on the development of CCP following SCI. Three commonly used outbred strains of rats were selected: Long-Evans, Wistar, and Sprague-Dawley. Responses to mechanical and thermal stimulation, as well as locomotor recovery were compared between strains and models before (baseline) and after SCI.

MATERIALS AND METHODS

Experimental Animals

Subjects were male Long-Evans, Wistar, and Sprague-Dawley rats, 100–125 g, obtained from Harlan Sprague-Dawley, Inc., housed with a light/dark cycle of 12 h/12 h, and fed *ad libitum*. Experimental procedures were re-

viewed by the UTMB Animal Care and Use Committee and were consistent with the NIH Guide for the Care and Use of Laboratory Animals. Twenty-five animals from each strain were divided into either hemisection ($n = 10$ for each strain) or contusion spinal cord injury (SCI) groups ($n = 15$ for each strain). All subjects were acclimated to the behavioral testing environment and testing procedures for 5 days before data acquisition and showed no evidence of increased responsiveness or learning during presurgical testing.

Contusion Injury

Spinal cord contusion injury was produced as previously described (Gruner, 1992; Huang and Young, 1994; Hulsebosch et al., 2000). Briefly, subjects were anesthetized by an intraperitoneal injection of pentobarbital (40 mg/kg). Anesthesia was considered complete when there was no flexor withdrawal in response to noxious foot pinch. The subjects' backs were shaven, an incision made to expose the vertebral column, and a laminectomy was performed at spinal segment T10. Spinal cord injury was produced using the New York University (NYU) injury device. A 10-g weight, 2.0 mm in diameter, was dropped from 12.5 mm onto the exposed cord. Following spinal injury, muscle and fascia were sutured, the skin autoclipped, and the animals were allowed to recover from anesthesia. Postoperative treatments included 0.9% saline (1.0 mL subcutaneously) for rehydration and a prophylactic antibiotic (Baytril, 30 mg/kg, subcutaneously) was given twice daily until bladder control returned. Bladders were manually expressed twice daily until automatic bladder control recovered, usually by 10 days following injury.

Hemisection Injury

Subjects were deeply anesthetized by intraperitoneal injection of sodium pentobarbital (40 mg/kg), and the left side of the spinal cord was hemisected as previously described (Christensen et al., 1996; Hains et al., 2000). Briefly, a laminectomy was performed at T11, the lumbar spinal cord was identified with the accompanying dorsal vessel, and the spinal cord hemisected at T13, with a no. 11 scalpel blade without damage to the dorsal spinal artery or branches. Iridectomy scissors were used to ensure the completeness of the hemisection. Muscle and fascia were sutured closed, the skin closed with autoclips, and animals were allowed to recover from anesthesia. Postoperative treatments included 0.9% saline (1.0 mL subcutaneously) for rehydration and penicillin-G (0.35 mL/kg intramuscular) as a prophylactic antibiotic. The hemisection lesion was confined unilaterally and included the dorsal column, Lissauer's tract, lateral and

ventral column systems, and gray matter. Animals that demonstrated a decrement in locomotor function of the contralateral hindlimb, indicating an over-hemisection, were excluded from the study.

Locomotor Function

Locomotor function was evaluated using the Basso, Beattie, and Bresnahan (BBB) open-field locomotor test (Basso et al., 1995). Briefly, the BBB scale ranges from 0 (no hindlimb movement) to 21 (normal movement-coordinated gait with parallel paw placement). Scores from 0 to 7 indicate the return of isolated movements in the three joints (hip, knee, and ankle). Scores from 8 to 13 indicate the return of paw placement and coordinated movements with the forelimbs. Scores from 14 to 21 show the return of toe clearance during stepping, predominant paw position, trunk stability, and tail position. BBB scores were measured before injury (baseline) and on postinjury days (PID) 1 through 14, 21, 28, and 35.

Mechanical Stimuli

Paw withdrawal frequency in response to repeated mechanical stimuli to the glabrous surface of the forelimbs and hindlimbs was used to quantify mechanical sensitivity. In this test, the frequency of paw withdrawals in response to graded mechanical stimuli (4.79, 9.96, and 204.1 mN and pin) was recorded prior to injury and at PID 7, 14, 21, 28, and 35 as previously described (Choi et al., 1994; Christensen and Hulsebosch, 1997). The frequency of paw withdrawals to von Frey filament stimulation in each of 10 trials was repeated for each limb. Data is expressed as a difference in response frequency (percent of paw withdrawals after injury minus percent of paw withdrawals before injury) for between group comparisons. Since a change in absolute number of withdrawals to a stimulus may indicate an increase in the spinal reflex and not development of allodynia, only withdrawals accompanied by supraspinal behaviors (e.g., head turning to attend to the stimulus or biting the von Frey filament) were counted as a response. Following injury, hindlimb responses to mechanical stimulation for each of the strains was too variable to draw any conclusions; therefore, these data are not included in the analysis. The development of mechanical allodynia for individual subjects was defined by a statistically significant increase in the number of withdrawals to all strengths of von Frey stimulation on PID 35 compared to baseline ($p < 0.05$).

Thermal Stimuli

Forelimb and hindlimb paw withdrawal latency to a heat stimuli was measured using methods previously de-

scribed (Bennet and Xie, 1988; Dirig et al., 1997; Hargreaves et al., 1988) prior to injury and on PID 7, 14, 21, 28, and 35. Briefly, the rats were placed on a glass plate over a light box, and a radiant heat stimulus was applied by aiming a beam of light through a hole in the light box onto the glabrous surface of the paw of each limb through the glass plate. The light beam was turned off automatically by a photocell when the rat lifted the limb, allowing the measurement of time between the start of the light beam and the paw withdrawal. This time is defined as the paw withdrawal latency. Five minutes were allowed between each trial, and three measurements were averaged for each limb before injury (baseline) and on PID 7, 14, 21, 28, and 35. Values were normalized to zero for baseline and reported as change, in seconds, from baseline. Following injury, hindlimb responses to thermal stimulation for each of the strains was too variable to draw any conclusions; therefore, these data are not included in the analysis. The development of thermal allodynia for individual subjects was defined as a statistically significant decrease in paw withdrawal latencies compared to baseline on PID 35 ($p < 0.05$).

Statistical Analysis

Baseline behavioral measures for mechanical and thermal responses were compared between each strain using a one way analysis of variance (ANOVA). A one way repeated measures ANOVA was used to test for significant differences between each strain for mechanical and thermal responses following injury. *Post hoc* comparisons were made using Fisher's LSD test. The Wilcoxon rank sum test was used for nonparametric analysis of BBB scores. We used an alpha level of significance at 0.05 for all statistical tests. Data are expressed as means \pm standard error of the mean (SEM).

RESULTS

Baseline Responses to Mechanical and Thermal Stimuli

There were no strain differences in baseline responses to a 4.79 mN von Frey mechanical stimulation (Fig. 1A). Baseline values for 4.79 mN von Frey stimulation were 5.5 ± 0.5 , 6.5 ± 0.7 , and 6.3 ± 1.0 (percentage withdrawals) for Long-Evans, Wistar, and Sprague-Dawley, respectively. However, baseline responses to 9.96 mN von Frey mechanical stimulation demonstrated a significant difference between Long-Evans and Wistar rats ($p < 0.02$) and between Long-Evans and Sprague-Dawley rats ($p < 0.05$). Baseline values for 9.96 mN von Frey stimulation were 11.7 ± 1.0 , 16.5 ± 1.4 , and 16.0 ± 1.8 (percentage withdrawals) for Long-Evans, Wistar, and

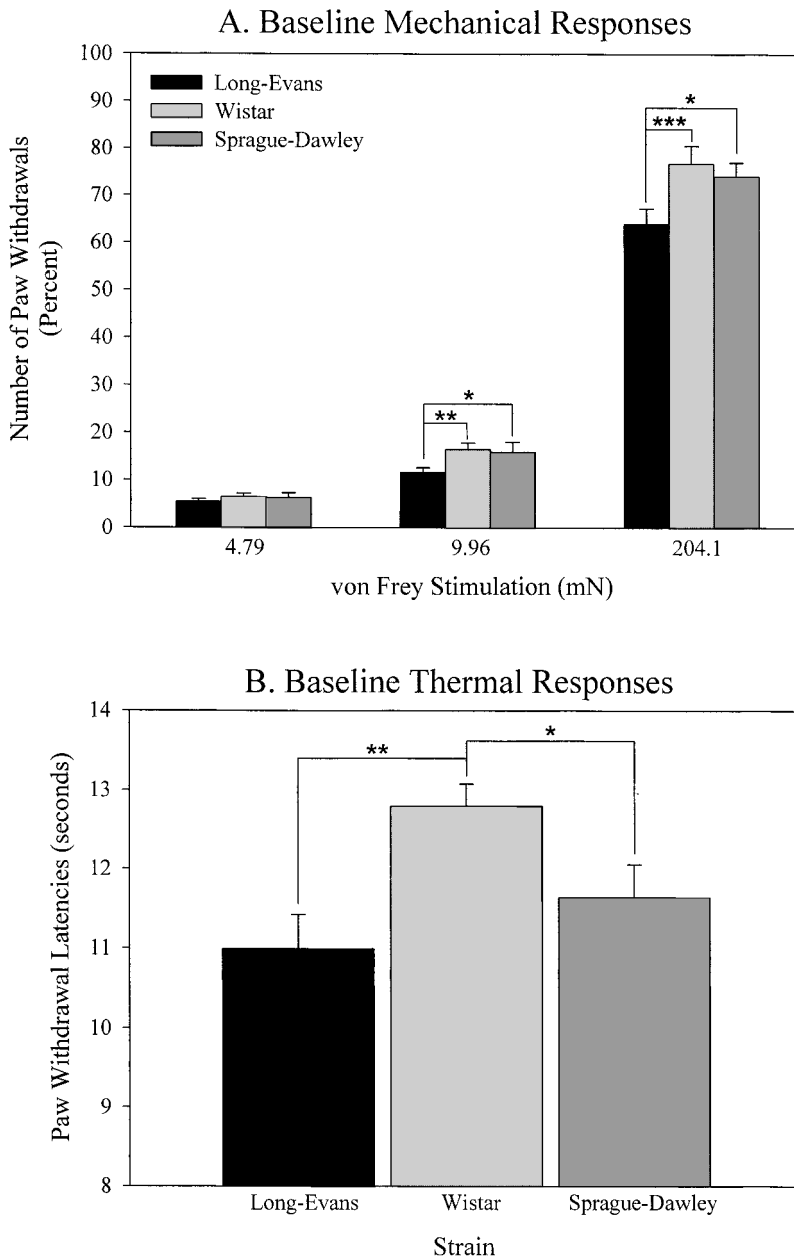


FIG. 1. Baseline forelimb paw withdrawal responses, expressed as percentage, to von Frey filament (4.79, 9.96, and 204.1 mN) stimulation (**A**) and baseline forelimb paw withdrawal latencies to thermal stimulation (**B**). Long-Evans rats consistently show lower baseline responses to mechanical and thermal stimulation, while Wistar rats consistently have the highest baseline responses to measures of both mechanical and thermal stimulation. Data are plotted as means \pm SEM (* = $p < 0.05$; ** $p < 0.02$; *** $p < 0.01$).

Sprague-Dawley rats, respectively. Responses to 204.1 mN von Frey stimulation also revealed a significant decrease for Long-Evans rats compared to Wistar ($p < 0.01$) and Sprague-Dawley rats ($p < 0.05$). Baseline responses to 204.1 mN von Frey stimulation were 63.9 ± 3.4 , 76.7 ± 3.9 , and 74.0 ± 3.0 (percentage withdrawals)

for Long-Evans, Wistar, and Sprague-Dawley rats, respectively.

Responses to thermal stimulation also revealed strain differences in baseline values (Fig. 1B). Wistar rats demonstrated longer baseline paw withdrawal latencies compared to Long-Evans ($p < 0.002$) and Sprague-Daw-

ley rats ($p < 0.05$). Baseline paw withdrawal latencies to thermal stimulation were 11.0 ± 0.4 , 12.8 ± 0.3 , and 11.6 ± 0.4 sec for Long-Evans, Wistar, and Sprague-Dawley rats, respectively.

Percentages of Animals Developing Allodynia

Following contusion SCI, each strain displayed a difference in the percentages of animals that developed mechanical and thermal allodynia (Fig. 2A). Long-Evans

rats displayed the highest percentages of the three strains to develop mechanical allodynia (11/15, 73%), while only 60% developed thermal allodynia (9/15). Sixty percent (9/15) of the Wistar strain developed mechanical allodynia following contusion SCI, while 80% (12/15) developed thermal allodynia. Sixty percent (9/15) of the Sprague-Dawley strain developed mechanical allodynia, with 87% (13/15) developing thermal allodynia.

Subjects in the hemisection model of SCI also demonstrated strain differences in the development of mechan-

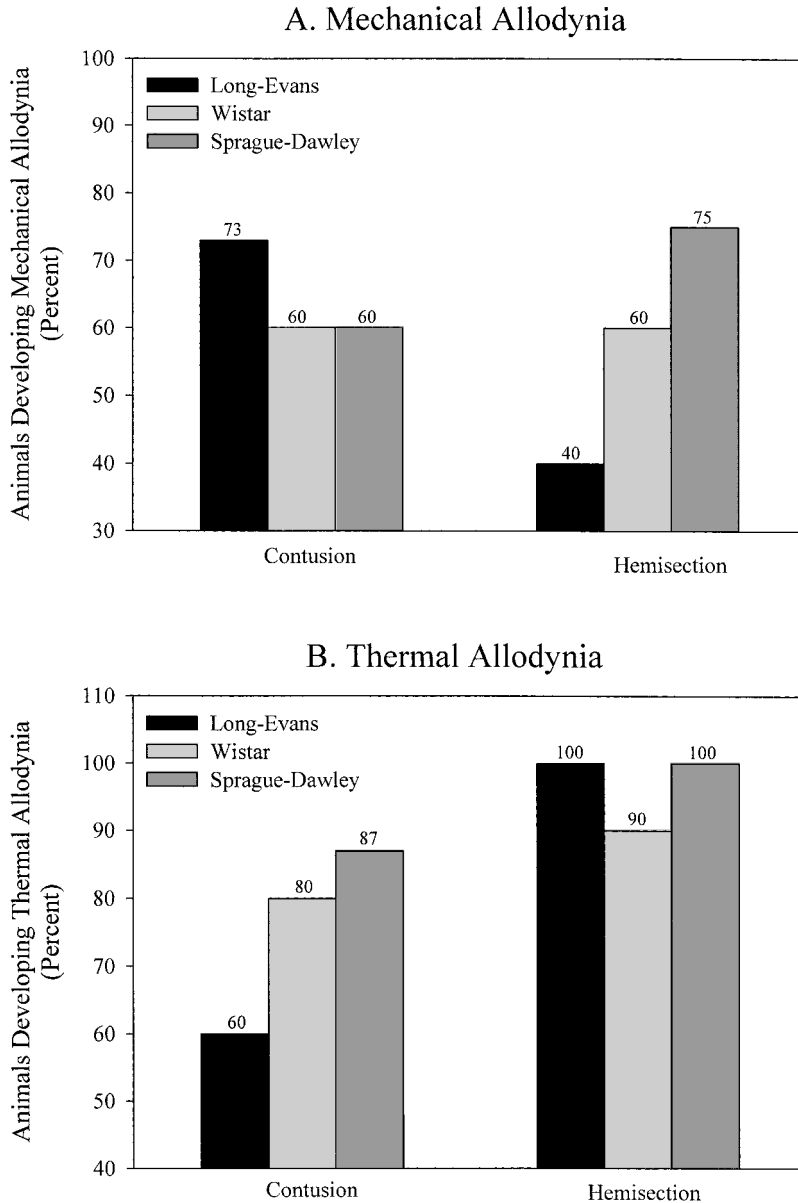


FIG. 2. Bar graph representing the percentages of each strain that developed mechanical (A) or thermal (B) allodynia following contusion or hemisection SCI. The percentage is indicated above each bar. Overall, Sprague-Dawley rats in the hemisection model produced more animals that developed both mechanical and thermal allodynia.

ical and thermal allodynia (Fig. 2B). Long-Evans rats displayed the lowest percentage of subjects to develop mechanical allodynia (4/10, 40%); however, 100% developed thermal allodynia (10/10). Sixty percent (6/10) of the Wistar strain developed mechanical allodynia following hemisection SCI, while 90% developed thermal allodynia (9/10). Seventy-five percent (6/8) of the Sprague-Dawley strain developed mechanical allodynia, and 100% (8/8) developed thermal allodynia. For both models, each animal that developed mechanical allodynia also developed thermal allodynia, except for the Long-Evans strain in the contusion model. Only the animals that developed mechanical and thermal allodynia were included in this study.

Locomotor Function

All strains in the contusion SCI group had baseline BBB scores of 21.0 ± 0.0 (Fig. 3A). On PID 1, each strain in the contusion group had little to no hindlimb movement as indicated by BBB scores of 0.5 ± 0.2 , 0.7 ± 0.2 , and 0.7 ± 0.2 for Long-Evans, Wistar, and Sprague-Dawley rats, respectively. However, by PID 4, Sprague-Dawley rats had significantly higher ($p < 0.05$) BBB scores than the other strains. Wistar rats initially recovered faster than Long-Evans, but by PID 12 there was no difference between Wistars or Long-Evans rats. BBB scores for each strain slowly rose through PID 14 where values stabilized through PID 35. On PID 35, BBB scores were 12.1 ± 0.7 , 13.8 ± 1.4 , and 16.0 ± 1.0 for Long-Evans, Wistar, and Sprague-Dawley rats, respectively.

Each strain in the hemisection SCI group had baseline BBB scores of 21.0 ± 0.0 (Fig. 3B). Following hemisection on PID 1, all strains had little to no movement of the ipsilateral hindlimb as indicated by BBB scores of 0.3 ± 0.3 , 0.3 ± 0.2 , and 0.3 ± 0.2 for Long-Evans, Wistar, and Sprague-Dawley rats, respectively. Each group slowly recovered through PID 14 with scores stabilizing on PID 14 through PID 35. On PID 3 through PID 10, Wistar and Sprague-Dawley rats demonstrated higher BBB scores than Long-Evans rats, with Sprague-Dawley rats remaining consistently higher than Long-Evans rats through PID 28. Long-Evans rats had consistently lower BBB scores at all time points measured. BBB scores on PID 35 were 15.0 ± 0.4 , 15.6 ± 1.6 , and 17.0 ± 1.2 for Long-Evans, Wistar, and Sprague-Dawley rats, respectively.

Mechanical Allodynia

Following contusion SCI, all strains demonstrated a temporal development of mechanical allodynia as indicated by an increase in forelimb withdrawals to graded von Frey stimulation (Fig. 4A,C,E). Responses to 4.79

mN von Frey stimulation slowly increased similarly for each strain to reach values of 19.1 ± 1.0 , 24.5 ± 2.2 , and 22.9 ± 1.7 (percentage withdrawals) on PID 35 for Long-Evans, Wistar, and Sprague-Dawley, respectively (Fig. 4A). A similar pattern was seen for 9.96 mN von Frey stimulation; values were 22.1 ± 3.3 , 24.3 ± 1.4 , and 23.8 ± 2.0 (percentage withdrawals) on PID 35 for Long-Evans, Wistar, and Sprague-Dawley rats, respectively (Fig. 4C). For 204.1 mN von Frey stimulation, values were 21.4 ± 2.1 , 21.9 ± 1.9 , and 20.7 ± 2.7 (percentage withdrawals) for Long-Evans, Wistar, and Sprague-Dawley rats respectively (Fig. 4E). Each strain responded 100% of the time to pin stimulus at each time point measured (data not shown).

Following hemisection SCI, all strains demonstrated a temporal development of mechanical allodynia as indicated by an increase in paw withdrawals to graded von Frey stimulation (Fig. 4B,D,F). Responses to 4.79 mN von Frey stimulation slowly increased similarly for each strain to reach values of 14.2 ± 3.5 , 18.3 ± 6.0 , and 15.8 ± 1.5 (percentage withdrawals) on PID 35 for Long-Evans, Wistar, and Sprague-Dawley, respectively (Fig. 4B). A similar pattern was seen for 9.96 mN von Frey stimulation; values were 20.4 ± 2.1 , 26.3 ± 4.3 , and 18.3 ± 5.8 (percentage withdrawals) on PID 35 for Long-Evans, Wistar, and Sprague-Dawley rats, respectively (Fig. 4D). For 204.1 mN von Frey stimulation, values were 32.3 ± 2.0 , 37.1 ± 6.0 , and 27.5 ± 3.2 (percentage withdrawals) for Long-Evans, Wistar, and Sprague-Dawley rats, respectively (Fig. 4F). Each strain responded 100% of the time to pin stimulus at each time point measured (data not shown).

Thermal Allodynia

Following contusion injury each strain demonstrated a gradual decrease in forelimb withdrawal latencies to thermal stimulation, indicating the development of thermal allodynia (Fig. 5). On PID 35, in the contusion model of SCI, paw withdrawal latencies had decreased by 3.7 ± 1.1 , 3.8 ± 1.3 , and 4.3 ± 1.3 sec for Long-Evans, Wistar, and Sprague-Dawley rats, respectively (Fig. 5A). A similar, albeit not as robust, development of thermal allodynia was seen in the hemisection model of SCI (Fig. 5B). Forelimb withdrawal latencies on PID 35 were 1.6 ± 0.5 , 2.8 ± 0.8 , and 3.4 ± 0.8 sec for Long-Evans, Wistar, and Sprague-Dawley rats, respectively.

DISCUSSION

The present study examines baseline responses to mechanical and thermal stimulation in three outbred strains of rats: Long-Evans, Wistar, and Sprague-Dawley. Ad-

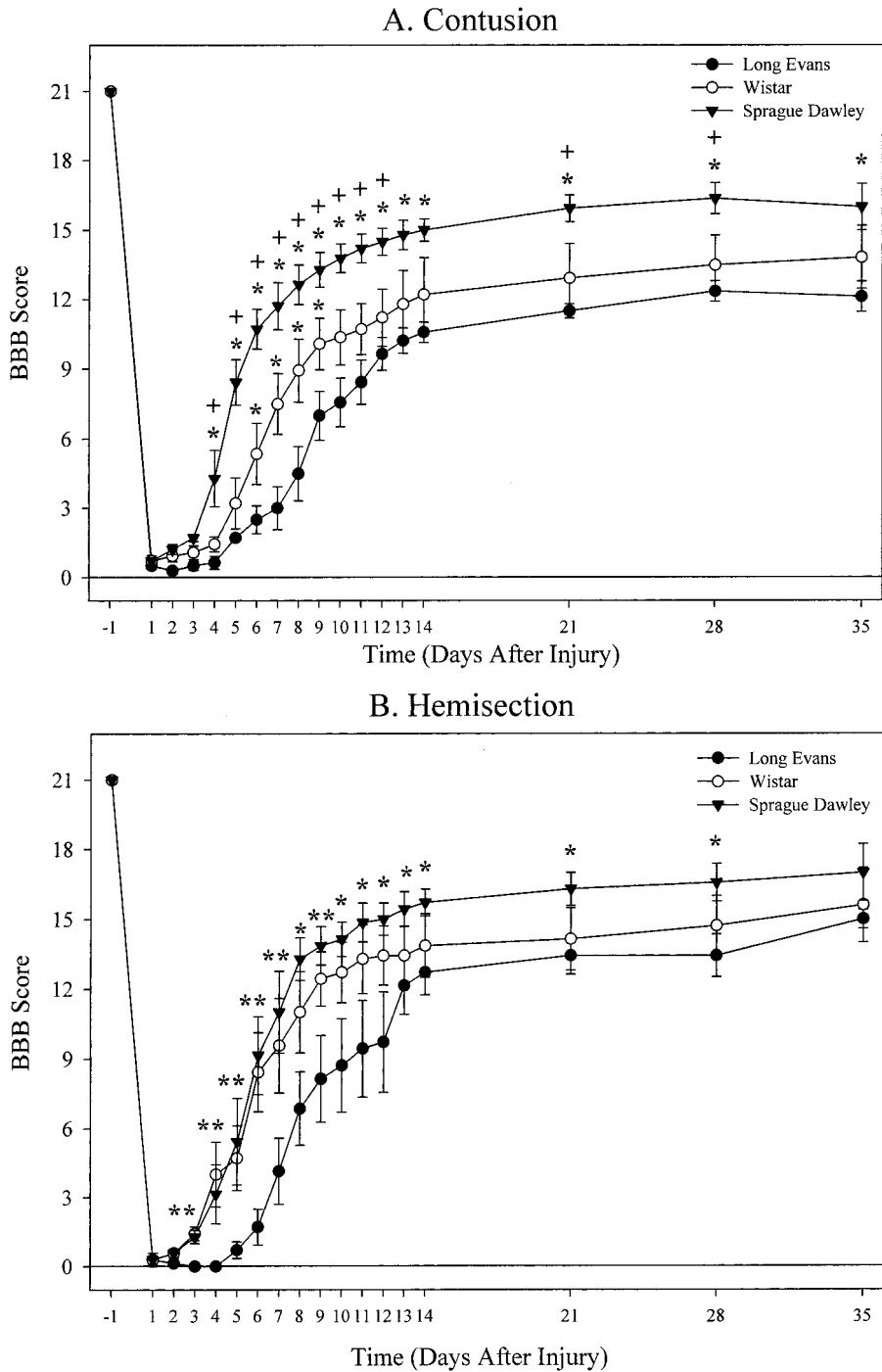


FIG. 3. BBB locomotor recovery scores for combined hindlimbs in the contusion model (A) and for the ipsilateral hindlimb in the hemisection model (B). For each model, the Sprague-Dawley rats recovered faster and to a greater extent than the other two strains. The rank order of recovery for each model was Sprague-Dawley > Wistar > Long-Evans; however, each strain displayed a similar temporal pattern of recovery. Data are expressed as means \pm SEM. *Statistically significant difference compared to Long-Evans ($p < 0.05$); + statistically significant difference compared to Wistar ($p < 0.05$).

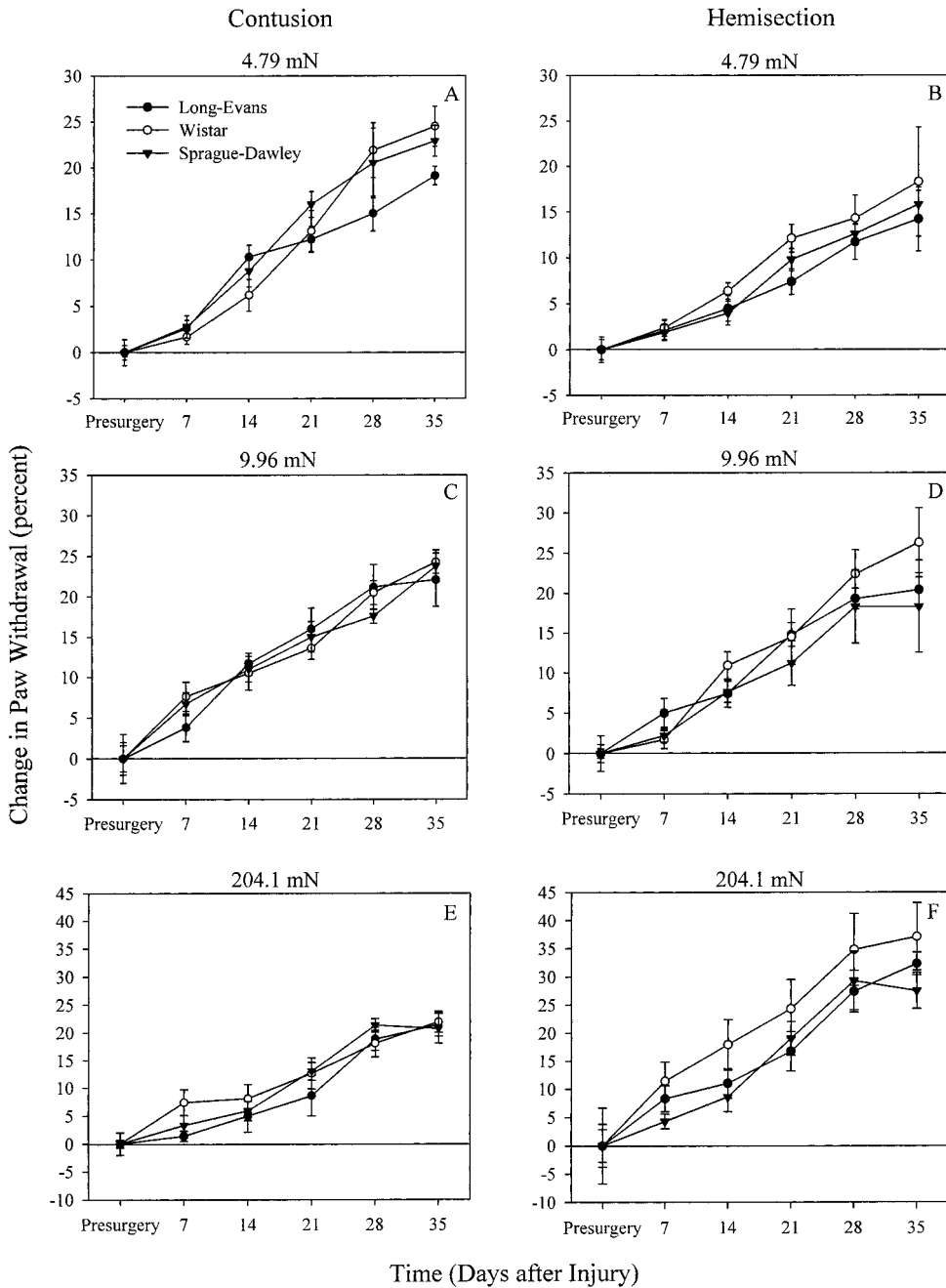


FIG. 4. Forelimb paw withdrawal responses, expressed as percentage change from baseline, to von Frey filament (4.79, 9.96, and 204.1 mN) stimulation in the contusion (A, C, E) and hemisection (B, D, F) models. A similar temporal pattern for the development of mechanical allodynia is seen in all three strains. However, Sprague-Dawley rats in the hemisection model appear to have more robust responses, especially at 204.1 mN stimulation. Each strain responded 100% of the time to pin stimulation before and after injury for each model (data not shown). Data are expressed as means \pm SEM.

ditionally, individual strains were examined for the development of mechanical and thermal allodynia, and locomotor recovery in two separate models of SCI. Overall, Wistar rats displayed greater responsiveness to mechanical and thermal stimulation in baseline responses

compared to the other two strains. Long-Evans rats displayed the lowest responsiveness of the three strains to both mechanical and thermal stimulation. In both contusion and hemisection models of SCI, the rank order of magnitude in locomotor recovery was Sprague-Daw-

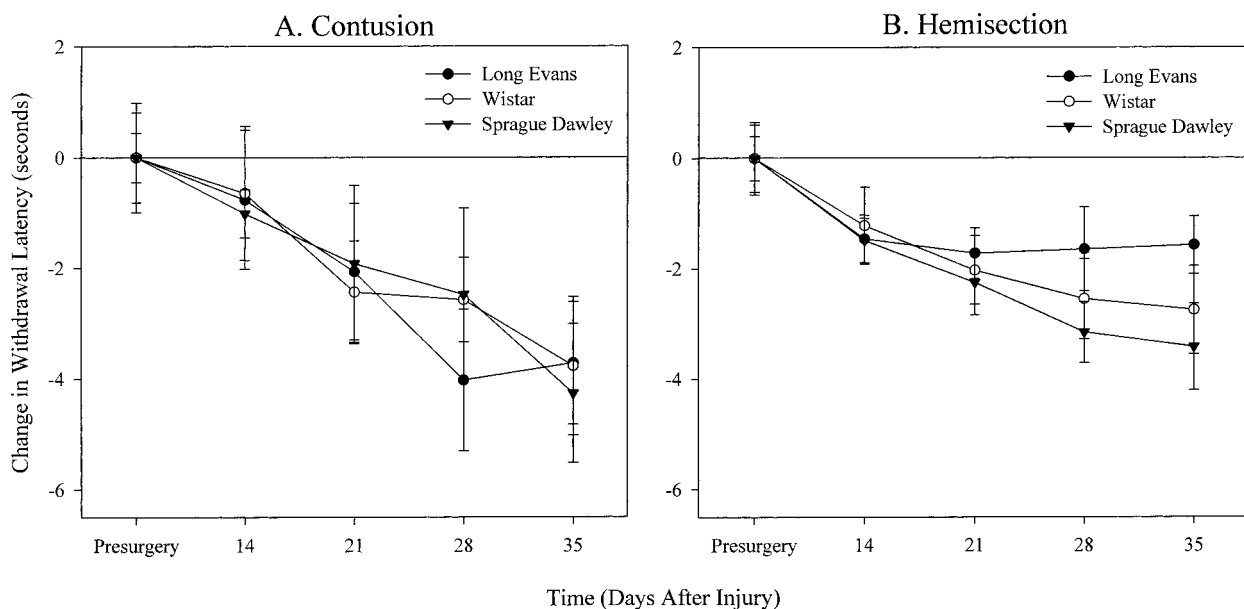


FIG. 5. Forelimb paw withdrawal latencies to thermal stimulation in the contusion (A) and hemisection (B) models of SCI expressed as change in seconds from baseline. Each strain in each model demonstrated the same temporal pattern of development of thermal allodynia. While the hemisection model had a more rapid onset, the contusion model produced slightly more robust responses. Data are expressed as means \pm SEM.

ley > Wistar > Long-Evans. While each strain developed mechanical allodynia in a similar temporal pattern, the hemisection model produced a more robust response in general; however, the contusion model of SCI produced a more pronounced thermal allodynia. Overall, the Sprague-Dawley strain produced the most subjects to develop mechanical and thermal allodynia, with the hemisection model generating larger percentages than the contusion model.

Strains and Pains

It has become apparent that there is a strain-dependency on the development of pain-like syndromes in experimental models. However, there are some strains that appear to be more responsive than others. For example, Sprague-Dawley rats have shorter tail withdrawal latencies to a hot water bath than Long-Evans or Wistar Kyoto rats (Mogil et al., 2000). Furthermore, in a spinal nerve ligation model of neuropathic pain, Sprague-Dawley rats demonstrate higher levels of pain-like behaviors than Long-Evans rats (Yoon et al., 1999). Our results show that Sprague-Dawley rats have higher baseline responses to mechanical stimulation compared to Long-Evans rats, which is in agreement with previous reports. However, our results are in contrast to a study on strain differences in a sciatic nerve ligation model examining neuropathic hyperalgesia (Lovell et al., 2000), where it

was reported that there were no significant differences between Wistar and Sprague-Dawley rats in baseline or post ligation measures of thermal hyperalgesia. In contrast, we found a significant increase in baseline thermal responses for Wistars compared to Sprague-Dawley rats. One possible explanation for the observed difference is that the rats were purchased from different vendors, which maintain separate breeding populations. It has been shown that Sprague-Dawley rats from different vendors demonstrated different levels of pain-like behaviors following spinal nerve ligation (Yoon et al., 1999), which may be provided in part by differences in central noradrenergic projections and functions (Clark and Proudfit, 1992; Clark et al., 1991; West et al., 1993). Another possible explanation is that there were diet differences between the rats in each study. Shir et al. (1998) have shown that a diet free of soy greatly enhances the degree of mechanical and thermal allodynia following sciatic nerve ligation. Animals in the current study were fed soy free rat chow. Another consideration for inter-strain differences in baseline measures of mechanical and thermal responsiveness is that each strain may have different physical characteristics, such as plantar skin thickness and/or blood flow (Shir et al., 1991; Yoon et al., 1999).

It has been suggested that different strains may undergo different levels of central sensitization (Luo and Wiesenfeld-Hallin, 1994; Yoon et al., 1999); however, in the current study, each strain developed mechanical and

thermal allodynia in a similar temporal pattern with only slight differences in magnitude. In the three outbred strains examined in the present study, mechanisms that lead to mechanical and thermal allodynia may be similar. It should be noted that not each strain develops these markers of central sensitization in an equal fashion.

Models of Spinal Cord Injury and Chronic Central Pain

There are several models used to study CCP in SCI (Ramer et al., 2000; Vierck et al., 2000). Two models of CCP induced by SCI currently being used in our laboratory are the contusion and hemisection models (Christensen and Hulsebosch, 1997; Hains et al., 2000; Hulsebosch et al., 2000; Mills et al., 2001a). Each model has strengths and weaknesses, some of which are highlighted by the results of the present study.

The contusion model of SCI may more closely parallel the types of spinal injury that occurs in the patient population (Bunge, 1994; Bunge et al., 1993; Ramer et al., 2000). Most injuries in humans are produced by vertebral or disc displacement that impinges upon the spinal cord (Ramer et al., 2000). The development and widespread use of the NYU impactor has helped to standardize the contusion model of SCI (Basso et al., 1996; Constantini and Young, 1994; Gruner, 1992; Hulsebosch et al., 2000; Magnuson et al., 1999; Metz et al., 2000; Mills et al., 2001a). However, this type of model makes it difficult to compare postinjury neuronal survival vs. regeneration of damaged axons. Moreover, the present study shows that not every animal, regardless of strain, develops mechanical and thermal allodynia after contusion injury. Thus, time, effort, and money, are spent on animals that will have to be removed and replaced. Furthermore, rats receiving the contusion injury require substantial postinjury care, most notably, manual bladder expression twice daily with prophylactic treatment for the development of urinary tract infections.

Not all spinal injuries result from disc or vertebral dislocations. Stabbings, gunshot wounds, and other forms of penetrating trauma contribute to spinal cord injury etiology. As such, the hemisection injury model is better suited to model these types of injuries. The hemisection model allows for selective surgical elimination and study of individual pathways (specific tracts) for regeneration and cell survival (Ramer et al., 2000). The present study demonstrates that in the hemisection model, almost every animal develops thermal allodynia; however, lower percentages develop mechanical allodynia depending on strain. Thus, time and effort may be expended on animals that will not develop pain-like syndromes if care is not given to strain selection (consider that only 40% of

Long-Evans rats develop mechanical allodynia). The hemisection model has the additional advantage of surgical ease (no weight-drop apparatus needed) and no large demands on postinjury animal care.

Both the contusion and hemisection models suffer from another drawback when compared to human SCI. Each model requires direct dorsal access to the cord via a laminectomy; however, most human injuries in humans occur within the "closed" vertebral system, which may result in ventral or circumferential cord compression (Ramer et al., 2000). While each model has its shortcomings, it should be noted that the results from this study demonstrate an important quality of both, namely that regardless of strain, those animals which do develop CCP syndromes, do so in a similar temporal fashion. There are many mechanisms proposed to explain the altered behavioral states and the development of CCP after SCI, ranging from structural alterations (Hulsebosch and Coggeshall, 1981a,b; Krenz and Weaver, 1998; Krenz et al., 1999; McNeill et al., 1990, 1991) to excitatory amino acid receptor-mediated changes (Bennett et al., 2000; Grossman et al., 1999, 2000; Hulsebosch et al., 2000; Mills et al., 2000, 2001b,c; Woolf and Thomson, 1991; Wrathall et al., 1997) and loss of tonic descending inhibitory control (Hains et al., 2001; Sweet, 1991). Since mechanical and thermal allodynia can be separated etiologically and/or pharmacologically, it appears that two separate mechanisms may mediate the development of these modalities (Bennett et al., 2000; Mills et al., 2001b; Sluka and Willis, 1997; Sluka et al., 1997), and it appears that these separate mechanisms may be similar across each strain examined in this study.

One concern regarding withdrawals to evoked stimuli, such as von Frey or thermal stimulation, is that the responses may be learned and therefore withdrawals would occur more frequently or more rapidly with repeated tests. This is unlikely for several reasons: (1) not all animals displayed a change in response frequency or withdrawal latencies after surgery; (2) animals were acclimated and tested for several days/trials before data collection began and demonstrated no evidence of increased responsiveness prior to surgery; and (3) no change in withdrawal frequency occurred over time in naive or sham animals using the testing paradigms of the present study (Christensen et al., 1996). Another confound in the behavioral analysis is that differences in locomotor ability following the contusion injury for the three rat strains may be due to histopathological differences between the strains (i.e., differences in lesion volumes). The lesion produced by the moderate level of contusion injury used here results in an incomplete SCI that is consistent in lesion volume measures (Mills et al., 2001b). The extent of actual tissue loss is confined mainly to T10 with slight en-

crouchment into T9 (caudal portion) and T11 (rostral portion) affecting predominately the ventral portion of the dorsal funiculus (corticospinal region) and central gray matter. While lesion parameters, such as gray and white matter sparing have been well described, it should be noted that some studies have shown preferential changes in susceptibility to cell death in specific cell types following contusion injury (Grossman et al., 1999; Qiu et al., 2001). It is possible that specific strains of rats may have populations or subpopulations of cells that are more susceptible to injury, which contribute to differential behavioral outcomes. Thus, a detailed examination of cell specific loss in different strains following SCI is warranted for future studies.

Animals that exhibit both mechanical and thermal allodynia of the forelimbs, also demonstrate a bilateral band of mechanical allodynia at, and rostral to, the segmental level of injury (Christensen and Hulsebosch, 1997; Hulsebosch et al., 2000). This observation is in agreement with other models of SCI and of patient reports (Tasker and Dostrovsky, 1989). For example, in the quisqualic acid excitotoxic lesion model of SCI (Yeziarski, 2000), unilateral overgrooming/autotomy develops in dermatomes that border the lesion. It should be noted that overgrooming/autotomy indicates the presence of abnormal tonic sensations rather than anesthesia (Kauppila, 1998). Monkeys and rats both demonstrate overgrooming/autotomy following lesions of the anterolateral spinal column (Levitt and Levitt, 1981; Ovelmen-Levitt et al., 1995). Additionally, anterolateral cordotomy can produce allodynia and hyperalgesia in rats (Vierck and Light, 2000; Vierck et al., 1986) and humans (Bowsher, 1988). Pain-like behaviors are also seen following photochemically induced ischemic spinal lesions (Hao et al., 1991; Wiesenfeld-Hallin et al., 1997; Xu et al., 1992). Furthermore, our results demonstrating that not every animal develops mechanical or thermal allodynia is consistent with previous reports in other models (Xu et al., 1992).

CONCLUSION

In summary, the present study demonstrates that there are baseline behavioral differences in measures of mechanical and thermal stimulation between Long-Evans, Wistar, and Sprague-Dawley rats. Following SCI produced by contusion or hemisection, different percentages of each strain develop mechanical and thermal allodynia. In both contusion and hemisection models of SCI, the rank order of locomotor recovery was Sprague-Dawley > Wistar > Long-Evans. While each strain developed mechanical allodynia in a similar temporal pattern in both models, the hemisection model had a more

robust response in general. However, the contusion model of SCI produced a more pronounced thermal allodynia. Overall, the Sprague-Dawley strain produced the most subjects to develop mechanical and thermal allodynia, with the hemisection model generating larger percentages than the contusion model. These results suggest that strain selection has a greater impact on initial locomotor recovery and model selection has a greater impact on the development of CCP following SCI. There are several models of CCP induced by SCI and currently there appears to be no one model or strain which best parallels CCP in the human SCI patient. However, the use of different strains does demonstrate that genetic contributions play an important role in recovery following SCI.

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REFERENCES

- BALAZY, T.E. (1992). Clinical management of chronic pain in spinal cord injury. *Clin. J. Pain* **8**, 102–110.
- BASSO, M., BEATTIE, M.S., and BRESNAHAN, J.C. (1995). A sensitive and reliable locomotor rating scale for open field testing in rats. *J. Neurotrauma* **12**, 1–21.
- BASSO, D.M., BEATTIE, M.S., and BRESNAHAN, J.C. (1996). Graded histological and locomotor outcomes after spinal cord contusion using the NYU weight-drop device versus transection. *Exp. Neurol.* **139**, 244–256.
- BENNETT, G.J., and XIE, Y.K. (1988). A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. *Pain* **33**, 87–107.
- BENNETT, A.D., EVERAHART, A.W., and HULSEBOSCH, C.E. (2000). Intrathecal administration of an NMDA or a non-NMDA receptor antagonist reduces mechanical but not thermal allodynia in a rodent model of chronic central pain after spinal cord injury. *Brain Res.* **859**, 72–82.
- BERIC, A., DIMITRJEVIC, M.R., and LINDBLOOM, U. (1988). Central dysesthesias syndrome in spinal cord injury patients. *Pain* **34**, 39–48.
- BOIVIE, J. (1984). Disturbances in cutaneous sensibility in patients with central pain caused by the spinal cord lesions of syringomyelia. *Pain Suppl.* **2**, s82.
- BOWSHER, D. (1988). Contralateral mirror-image pain following anterolateral cordotomy. *Pain* **88**, 63–65.
- BUNGE, R.P. (1994). Clinical implications of recent advances

- in neurotrauma research, in: *The Neurobiology of Central Nervous System Trauma*. S.K. Salzman and A.I. Faden (eds), Oxford University Press: New York, pps. 328–339.
- BUNGE, R.P., PUCKETT, W.R., BECERA, J.L., et al. (1993). Observations on the pathology of human spinal cord injury. A review and classification of 22 new cases with details from a case of chronic cord compression with extensive focal demyelination, in: *Advances in Neurology*. Vol. 59. F.J. Seil (ed), Raven Press: New York, pps. 75–89.
- CAIRNS, D.M., ADKINS, R.H., and SCOTT, M.D. (1996). Pain and depression in acute traumatic spinal cord injury: origins of chronic problematic pain? *Arch. Phys. Med. Rehabil.* **77**, 329–335.
- CHOI, Y., YOON, Y.W., NA, H.S., et al. (1994). Behavioral signs of ongoing pain and cold allodynia in a rat model of neuropathic pain. *Pain* **59**, 369–376.
- CHRISTENSEN, M.D., EVERHART, A.W., PICKELMAN, J.T., et al. (1996). Mechanical and thermal allodynia in chronic central pain following spinal cord injury. *Pain* **68**, 97–107.
- CHRISTENSEN, M.D., and HULSEBOSCH, C.E. (1997). Chronic central pain after spinal cord injury. *J. Neurotrauma* **14**, 517–537.
- CLARK, F.M., and PROUDFIT, H.K. (1992). Anatomical evidence for genetic difference in the innervation of the rat spinal cord by noradrenergic locus coeruleus neurons. *Brain Res.* **591**, 44–53.
- CLARK, F.M., YEOMANS, D.C., and PROUDFIT, H.K. (1991). The noradrenergic innervation of the spinal cord: differences between two substrains of Sprague-Dawley rats determined using retrograde tracers combined with immunocytochemistry. *Neurosci. Lett.* **125**, 155–158.
- CONSTANTINI, S., and YOUNG, W. (1994). The effects of methylprednisolone and the ganglioside GM1 on acute spinal cord injury in rats. *J. Neurosurg.* **80**, 97–111.
- DAVIDOFF, G., and ROTH, E.J. (1991). Clinical characteristics of central (dysesthetic) pain in spinal cord injury patients, in: *Pain and Central Nervous System Disease: The Central Pain Syndromes*. K.L. Casey (ed), Raven Press: New York, pps. 77–83.
- DAVIDOFF, G., ROTH, E., GUARRACINI, M., et al. (1987). Functional limiting dysesthetic pain syndrome among spinal cord injury patients: a cross sectional study. *Pain* **29**, 39–48.
- DELEO, J.A., and RUTKOWSKI, M.D. (2000). Gender differences in rat neuropathic pain sensitivity is dependent on strain. *Neurosci. Lett.* **282**, 197–199.
- DIRIG, D.M., SALAMI, A., RATHBUN, M.L., et al. (1997). Characterization of variables defining hindpaw withdrawal latency evoked by radiant thermal stimuli. *J. Neurosci. Methods* **76**, 183–191.
- FENDER, C., FUJINAGA, M., and MAZE, M. (2000). Strain differences in the antinociceptive effect of nitrous oxide on the tail flick test in rats. *Anesth. Analg.* **90**, 195–199.
- GROSSMAN, S.D., WOLFE, B.B., YASUDA, R.P., et al. (1999). Alterations in AMPA receptor subunit expression after experimental spinal cord contusion injury. *J. Neurosci.* **19**, 5711–5720.
- GROSSMAN, S.D., WOLFE, B.B., YASUDA, R.P., et al. (2000). Changes in NMDA receptor subunit expression in response to contusive spinal cord injury. *J. Neurochem.* **75**, 174–184.
- GRUNER, J.A. (1992). A monitored contusion model of spinal cord injury in the rat. *J. Neurotrauma* **9**, 123–128.
- HAINS, B.C., CHASTAIN, K.M., EVERHART, A.W., et al. (2000). Transplants of adrenal medullary chromaffin cells reduce forelimb and hindlimb allodynia in a rodent model of chronic central pain after spinal cord hemisection injury. *Exp. Neurol.* **164**, 426–437.
- HAINS, B.C., EVERHART, A.W., FULLWOOD, S.D., et al. (2001). Changes in serotonin, serotonin transporter expression and serotonin denervation supersensitivity: involvement in chronic central pain after spinal hemisection in the rat. *Exp. Neurol.* (submitted).
- HAO, J.-X., XU, X.J., ALDSKOGIUS, H., et al. (1991). Allodynia-like effects in rat after ischaemic spinal cord injury photochemically induced by laser irradiation. *Pain* **45**, 175–185.
- HARGREAVES, K., DUBNER, R., BROWN, F., et al. (1988). A new and sensitive method for measuring thermal nociception in cutaneous hyperalgesia. *Pain* **32**, 77–88.
- HUANG, P.P., and YOUNG, W. (1994). The effects of arterial blood gas values on lesion volumes in a graded rat spinal cord contusion model. *J. Neurotrauma* **11**, 547–562.
- HULSEBOSCH, C.E., and COGGESHALL, R.E. (1981a). Quantitation of sprouting of dorsal root axons. *Science* **213**, 1020–1021.
- HULSEBOSCH, C.E., and COGGESHALL, R.E. (1981b). Sprouting of dorsal root axons. *Brain Res.* **224**, 170–174.
- HULSEBOSCH, C.E., XU, G.-Y., PEREZ-POLO, J.R., et al. (2000). Rodent model of chronic central pain after spinal cord contusion injury. *J. Neurotrauma* **17**, 1205–1217.
- JACK, T.M., and LLOYD, J.W. (1983). Long term efficacy of surgical cordotomy in intractable nonmalignant pain. *Ann. R. Coll. Surg.* **65**, 97–102.
- KAUPPILA, T. (1998). Correlation between autotomy behavior and current theories of neuropathic pain. *Neurosci. Biobehav. Rev.* **23**, 111–129.
- KRENZ, N.R., and WEAVER, L.C. (1998). Sprouting of primary afferent fibers after spinal cord transection in the rat. *Neuroscience* **85**, 443–458.
- KRENZ, N.R., MEAKIN, S.O., KRASSIOUKOUV, A.V., et al. (1999). Neutralizing intraspinal nerve growth factor

- blocks autonomic dysreflexia caused by spinal cord injury. *J. Neurosci.* **19**, 7405–7414.
- LEVITT, M., and LEVITT, J. (1981). The deafferentation syndrome in monkeys; dysesthesias of spinal origin. *Pain* **10**, 129–147.
- LOUBSER, P.G., and DONOVAN, W.H. (1996). Chronic pain associated with spinal cord injury, in: *Neurotrauma*. R.K. Narayan, J.E. Wilberger, and J.T. Povlishock (eds), McGraw Hill: New York, pps. 1311–1322.
- LOVELL, J.A., STUESSE, S.L., CRUCE, W.L.R., et al. (2000). Strain differences in neuropathic hyperalgesia. *Pharm. Biochem. Behav.* **65**, 141–144.
- LUNDQVIST, C., SIOSTEEN, A., BLOMSTRAND, C., et al. (1991). Spinal cord injuries—clinical, functional, and emotional status. *Spine* **16**, 78–83.
- LUO, L., and WIESENFELD-HALLIN, Z. (1994). Genetic factors may influence the development of spinal reflex hyperexcitability following sciatic nerve section in the rat. *Neurosci. Lett.* **169**, 122–125.
- MAGNUSON, D.S., TRINDER, T.C., ZHANG, Y.P., et al. (1999). Comparing deficits following excitotoxic and contusion injuries in the thoracic and lumbar spinal cord of the adult rat. *Exp. Neurol.* **156**, 191–204.
- MCNEILL, D.L., CARLTON, S.M., COGGESHALL, R.E., et al. (1990). Denervation induced intraspinal synaptogenesis of calcitonin gene-related peptide containing primary afferent terminals. *J. Comp. Neurol.* **296**, 263–268.
- MCNEILL, D.L., CARLTON, D.M., and HULSEBOSCH, C.E. (1991). Intraspinal sprouting of calcitonin gene-related peptide containing primary afferents after deafferentation in the rat. *Exp. Neurol.* **114**, 3221–3329.
- METZ, G.A., CURT, A., VAN DE MEENT, H., et al. (2000). Validation of the weight-drop contusion model in rats: a comparative study of human spinal cord injury. *J. Neurotrauma* **17**, 1–17.
- MILLS, C.D., XU, G.-Y., JOHNSON, K.M., et al. (2000). AIDA reduces glutamate release and attenuates mechanical allodynia after spinal cord injury. *Neuroreport* **11**, 3067–3070.
- MILLS, C.D., GRADY, J.J., and HULSEBOSCH, C.E. (2001a). Changes in exploratory behavior as a measure of central pain following spinal cord injury. *J. Neurotrauma* (in press).
- MILLS, C.D., JOHNSON, K.M., UNABIA, G.C., et al. (2001b). Group I metabotropic glutamate receptors in spinal cord injury: roles in neuroprotection and the development of chronic central pain. *J. Neurotrauma* (submitted).
- MILLS, C.D., FULLWOOD, S.D., and HULSEBOSCH, C.E. (2001c). Changes in metabotropic glutamate receptor expression following spinal cord injury. *Exp. Neurol.* (in press).
- MOGIL, J.S. (1999). Individual differences in pain: moving beyond the universal rat. *APS Bull.* **9**, 12–13.
- MOGIL, J.S., WILSON, S.G., BON, K., et al. (1999a). Heritability of nociception I: responses of 11 inbred mouse strains on 12 measures of nociception. *Pain* **80**, 67–82.
- MOGIL, J.S., WILSON, S.G., BON, K., et al., (1999b). Heritability of nociception II: types of nociception revealed by genetic correlation analysis. *Pain* **80**, 83–93.
- MOGIL, J.S., CHESLER, E.J., WILSON, S.G., et al. (2000). Sex differences in thermal nociception and morphine antinociception in rodents depend on genotype. *Neurosci. Biobehav. Rev.* **24**, 375–389.
- NEBERT, D.W., and WEBER, W.W. (1990). Pharmacogenetics, in: *Principles of Drug Action. The Basis of Pharmacology*. W.B. Pratt and P. Taylor (eds), Churchill Livingstone: New York, pps. 469–531.
- NOGUES, M.A. (1987). Syringomyelia and syringobulbia, in: *Handbook of Clinical Neurology. Vol. 50*. P.J. Vinken, G.W. Bruyn and H.L. Klawans (eds), Elsevier: Amsterdam, pps. 305–314.
- OVELMEN-LEVITT, J., GORECKI, J., NGUYEN, K., et al. (1995). Spontaneous and evoked dysesthesias observed in the rat after spinal cordotomies. *Sterotact. Funct. Neurosurg.* **65**, 157–160.
- PAGNI, C.A. (1989). Central pain due to spinal cord and brain stem damage, in: *Textbook of Pain, 2nd ed.* P.D. Wall and R. Melzack (eds), Churchill Livingstone: New York, pps. 634–655.
- QIU, J.-X., NESCI, O., YE, Z., et al. (2001). Bcl-x_L expression after contusion to the rat spinal cord. *J. Neurotrauma* (in press).
- RAMER, M.S., HARPER, G.P., and BRADBURY, E.J. (2000). Progress in spinal cord research; a refined strategy for the international spinal research trust. *Spinal Cord* **38**, 449–472.
- RICHARDS, J.S., MEREDITH, R.L., NEPOMUCENO, C., et al. (1980). Psycho-social aspects of chronic pain in spinal cord injury. *Pain* **8**, 355–366.
- RINTALA, D.H., LOUBSER, P.G., CASTRO, J., et al. (1998). Chronic pain in a community-based sample of men with spinal cord injury: prevalence, severity, and relationship with impairment, disability, handicap and subjective well-being. *Arch Phys. Med. Rehabil.* **79**, 604–614.
- SCHLIEP, G. (1978). Syringomyelia and syringobulbia, in: *Handbook of Clinical Neurology. Vol. 32*. P.J. Vinken and G.W. Bruyn (eds), North Holland: Amsterdam, pps. 255–327.
- SEGATORE, M. (1994). Understanding chronic pain after spinal cord injury. *J. Neurosci. Nurs.* **26**, 230–236.
- SHIR, Y., RATNER, A., DEVOR, M., et al. (1991). Mechano- and thermo-sensitivity in rats genetically prone to developing neuropathic pain. *Neuroreport* **2**, 313–316.

- SHIR, Y., RATNER, A., RAJA, S.N., et al. (1998). Neuropathic pain following partial nerve injury in rats is suppressed by dietary soy. *Neurosci. Lett.* **240**, 73–76.
- SLUKA, K.A., and WILLIS, W.D. (1997). The effects of G-protein kinase inhibitors on the behavioral responses of rats to intradermal injection of capsaicin. *Pain* **71**, 165–178.
- SLUKA, K.A., REES, H., CHEN, P.-S., et al. (1997). Capsaicin-induced sensitization of primate spinothalamic tract cells is prevented by a protein kinase C inhibitor. *Brain Res.* **772**, 82–86.
- SUDAKOV, S.K., BORISORV, E.V., and LYUPINA, Y.V. (1996). Influence of inheritance and fostering on sensitivity to effects of morphine on nociception and locomotor activity in two inbred rat strains. *Neuropharmacology* **35**, 1131–1134.
- SWEET, W.H. (1991). Deafferentation syndromes in humans: A general discussion, in: *Deafferentation Pain Syndromes: Pathophysiology and Treatment*. B.S. Nashold, Jr. and J. Ovelmen-Levitt (eds), Raven Press: New York, pps 259–283.
- TASKER, R.R., and DOSTROVSKY, J.O. (1989). Deafferentation and central pain, in: *Textbook of Pain*, 2nd ed. P.D. Wall and R. Melzack (eds), Churchill Livingstone: New York, pps. 154–180.
- VIERCK, JR., C.J. (1991). Can mechanisms of central pain syndromes be investigated in animal models? in: *Pain and Central Nervous System Disease: the Central Pain Syndromes*. K.L. Casey (ed), Raven Press: New York, pps. 129–141.
- VIERCK, JR., C.J., and LIGHT A.R. (2000). Allodynia and hyperalgesia within dermatomes caudal to a spinal cord injury in primates and rodents, in: *Nervous System Plasticity and Chronic Pain*. J. Sandkuhler, B. Bromm, and G. Gebhart (eds), Elsevier: Amsterdam, pps 411–428.
- VIERCK, JR., C.J., GREENSPAN, J.D., RITZ, L.A., et al. (1986). The spinal pathways contributing to the ascending conduction and the descending modulation of pain sensations and reactions, in: *Spinal Systems of Afferent Processing*. T. Yaksh (ed), Plenum: New York, pps. 275–329.
- VIERCK, JR., C.J., SIDDALL, P., and YEZIERSKI, P., (2000). Pain following spinal cord injury: animal models and mechanistic studies. *Pain* **89**, 1–5.
- WEST, W.L., YEOMANS, D.C., and PROUDFIT, H.K. (1993). The function of noradrenergic neurons in mediating antinociception induced by electrical stimulation of the locus coeruleus in two different sources of Sprague-Dawley rats. *Brain Res.* **626**, 127–135.
- WHITE, J. (1966). Cordotomy: assessment of its effectiveness and suggestions for its improvement. *Can. Neurosurg.* **13**, 1–19.
- WIESENFELD-HALLIN, Z., ALDSKOGIUS, H., GRANT, G., et al. (1997). Central inhibitory dysfunctions: mechanisms and clinical implications. *Behav. Brain Sci.* **20**, 420–425.
- WOOLF, C.J., and THOMPSON, S.W.N. (1991). The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. *Pain* **44**, 293–299.
- WRATHALL, J.R., TENG, Y.D., and MARRIOTT, R. (1997). Delayed antagonism of AMPA/kainite receptors reduces long-term functional deficits resulting from spinal cord trauma. *Exp. Neurol.* **145**, 565–573.
- XU, X.-J., HAO, J.-X., ALDSKOGIUS, H., et al. (1992). Chronic pain-related syndrome in rats after ischemic spinal cord lesion: a possible animal model for pain in patients with spinal cord injury. *Pain* **48**, 279–290.
- YEZIERSKI, R.P. (2000). Pain following spinal cord injury: pathophysiology and central mechanisms, in: *Progress in Brain Research*. J. Sandkuhler, B. Bromm, and G.F. Gebhart (eds), Elsevier: Amsterdam, pps. 429–449.
- YOON, Y.W., LEE, D.H., LEE, B.H., et al. (1999). Different strains and substrains of rats show different levels of neuropathic pain behaviors. *Exp. Brain Res.* **129**, 167–171.

Address reprint requests to:

Dr. Claire E. Hulsebosch

Department of Anatomy and Neuroscience

University of Texas Medical Branch at Galveston

Galveston, TX 77555–1043

E-mail: cehulseb@utmb.edu