

Consumption of Soy Diet before Nerve Injury Preempts the Development of Neuropathic Pain in Rats

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Background: A previous report using a partial sciatic nerve ligation (PSL) model for neuropathic pain in rats demonstrated that consumption of soy-containing diets preoperatively and postoperatively suppressed development of mechanical and heat allodynia, as well as hyperalgesia. The current study examined whether dietary soy suppresses these neuropathic sensory disorders when consumed either before or after PSL injury.

Methods: Male Wistar rats were grouped into seven different feeding regimens. These rats were fed SOY (RMH-1000, PMI Feeds, St. Louis, MO), a diet containing 85% soy protein since weaning, and were then switched to noSOY (Bio-Serv Co., Frenchtown, NJ), a diet devoid of soy at certain time points before PSL injury (14, 7, 1 days, or 15 and 0 h). Postoperatively, these rats were fed SOY or noSOY diets. Levels of mechanical and heat allodynia and hyperalgesia were determined preoperatively and 3, 8, and 14 days after PSL injury.

Results: Compared with groups fed preoperative noSOY, consumption of SOY before PSL injury significantly blunted postoperative levels of allodynia and hyperalgesia. Administering the SOY diet both before and after PSL injury provided no additional suppression of neuropathic pain. No pain suppression was noted in rats fed a noSOY diet preoperatively and SOY diet after PSL injury. Switching from SOY to noSOY feeding within 15 h of PSL injury was sufficient to allow for the full development of allodynia and hyperalgesia.

Conclusions: Consumption of a soy-containing diet suppressed the development of neuropathic pain after PSL injury. The pain-suppressing properties of dietary soy were the result of a preemptive effect (*i.e.*, when consumed preoperatively), but not a palliative effect (*i.e.*, when consumed postoperatively). This effect of soy-containing diets appears to be short-lived, since switching to a noSOY diet 15 h before ligation abrogated the suppressive effect of soy.

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PARTIAL nerve injury in humans may produce syndromes of neuropathic pain, typified by variable combinations of spontaneous pain, pain evoked by sensory stimuli (dysesthesia, allodynia, hyperalgesia, and hyperpathia), mirror image pain, and pain maintained by sympathetic output.¹ There are currently several animal models of neuropathic pain that mimic aspects of the clinical pain syndromes.² One of these models, unilateral partial sciatic nerve ligation (PSL) in rodents, produces long-lasting neuropathic sensory disorders, such as mechanical and heat allodynia and hyperalgesia, that depend on sympathetic activity.^{3,4}

Investigators using the same animal models have noted over the years that levels of chronic sensory disorders in rodents can vary considerably across different strains and selection lines, suggesting that genetic factors are at play.⁵ In addition, this variance has been attributed to various environmental factors such as temperature,⁶ barometric pressure,⁷ and diet.⁸

Previous experiments indicated that diet may influence the response of animals and humans to noxious stimuli. For example, heat pain in intact animals was attenuated by consumption of sucrose,⁹ increased fat content,¹⁰ and highly palatable foods.¹¹ Persistent hyperalgesia, produced by paw inflammation, was suppressed in rats consuming a diet rich in sucrose.¹² In a model of neuropathic pain after total denervation of the hind limb, consumption of a diet rich in tryptophan decreased levels of self-mutilation in rats.⁸ Using the same animal model, we reported that consumption of a diet based on casein was associated with suppression of pain-related behavior.¹³ In human subjects, tryptophan reduced pain sensitivity,¹⁴ enhanced morphine analgesia,¹⁵ and decreased chronic pain.¹⁶

We recently showed that consumption of soy-containing diets significantly suppressed the development of allodynia and hyperalgesia in rats after a PSL injury.¹⁷⁻¹⁹ In these experiments, rats were maintained on the tested diets for 2 weeks before PSL injury and throughout the postoperative observation period.¹⁷⁻¹⁹ However, it is currently not known whether dietary soy blunted neuropathic pain by acting as a preemptive or a palliative agent. Specifically, could soy serve as a suppressing agent for pain that has already developed (palliative effect), or does it exert its effect by preventing the development of neuropathic pain when consumed preoperatively (preemptive analgesia)? Therefore, in the current study we investigated whether feeding a soy-containing diet before or after nerve injury is essential

Table 1. Feeding Regimens of PSL-injured Rats

Groups	From Weaning until Study Onset	14 days before PSL	7 days before PSL	1 day before PSL	15 h before PSL		14 days after PSL
S14/S14*	SOY	SOY	SOY	SOY	SOY	↕ PSL injury↕	SOY
S14/noS14	SOY	SOY	SOY	SOY	SOY		noSOY
noS14/S14	SOY	noSOY	noSOY	noSOY	noSOY		SOY
noS14/noS14*	SOY	noSOY	noSOY	noSOY	noSOY		noSOY
noS7/noS14*	SOY	SOY	noSOY	noSOY	noSOY		noSOY
noS1/noS14*	SOY	SOY	SOY	noSOY	noSOY		noSOY
noS15h/noS14*	SOY	SOY	SOY	SOY	noSOY		noSOY

* Replicated experiment.

SOY = periods of feeding a soy-based diet; noSOY = periods of feeding a diet devoid of soy.

for suppressing the sensory disorders produced by PSL injury.

Materials and Methods

Animal Preparation

This study was approved by the Johns Hopkins University institutional animal care and use committee (Baltimore, MD) and conducted according to its regulations. Experiments adhered to the guidelines for animal experimentation of the International Association for the Study of Pain.

Experimental Animals. Twelve groups of male Wistar rats ($n = 8-10$ rats per group, including replication experiments) were used, each fed different feeding regimens. Rats, supplied by Harlan (Indianapolis, IA), weighed 225–275 g at the beginning of the experiment and were housed under standard colony conditions (3 rats per cage; ambient temperature, $22 \pm 0.5^\circ\text{C}$; water and food supplied *ad libitum*; day-night cycle, lights switched on at 7 AM and off at 7 PM). Animals were habituated to the conditions of the vivarium for 14 days before sensory testing. Tests were conducted between 10 AM and 5 PM.

Partial Sciatic Nerve Ligation Surgery. During inhalation anesthesia, the right sciatic nerve was exposed high on the thigh, near the trochanter. Using a minineedle, an 8-0 silk suture was inserted in the middle of the nerve, trapping in a tight ligation the dorsal one third to one half of the nerve thickness. The wound was closed layer by layer with muscle sutures, and the skin was stapled with Michel clips.

Diets and Feeding Regimens

Two diets were used: (1) SOY (RMH-1000; PMI Feeds, St. Louis, MO), a balanced diet comprising 14% protein (85% from soy), 67.5% carbohydrates, 6% fat, 4.5% fiber, 8% ash, vitamins, and trace elements, providing 3.3 Kcal/g; and (2) noSOY (Bio-Serv Co., Frenchtown, NJ), an artificial balanced diet²⁰ comprising 16% casein protein, 65% carbohydrates, 5% fat, 5% fiber, 3.5% ash, vitamins, and trace elements, providing 3.77 Kcal/g. All

rats were fed SOY diet from weaning until the beginning of the experiment.

Table 1 shows the study design, including duration of feeding periods with SOY or noSOY. Rats were randomly allocated to the following groups: group 1, SOY was administered for 14 days before PSL nerve injury and for 14 days thereafter (S14–S14 condition); group 2, SOY for 14 days before nerve injury and noSOY for 14 days thereafter (S14–noS14 condition); group 3, noSOY for 14 days before nerve injury and SOY for 14 days thereafter (noS14–S14 condition). The following four groups received noSOY for decreasing durations preoperatively and for 14 days after nerve injury: group 4, noSOY for 14 day before nerve injury and for 14 days thereafter (noS14–noS14 condition); group 5, noSOY for 7 days before nerve injury and for 14 days thereafter (noS7–noS14 condition); group 6, noSOY for 1 day before nerve injury and for 14 days thereafter (noS1–noS14 condition); group 7, rats were deprived of food for 12 h, then fed noSOY for 3 h before nerve injury and for 14 days thereafter (noS15h–noS14 condition). Groups 1 and 4–7 were replicated. Because the results of the replication run were not significantly different than the first run, data of corresponding groups in the two runs were pooled.

Behavioral Tests

After an acclimation period of 5 min to the testing environment, the responses of intact and PSL injured rats to mechanical and thermal stimuli were determined bilaterally. Tests were conducted 1 day before PSL surgery and repeated on days 3, 8, and 14 thereafter. The experimenter was blinded to the type of diet consumed by rats being tested, including the replication experiments.

Tactile sensitivity was measured with a set of 8 von Frey hairs (0.3, 1.1, 2.8, 4.4, 6.4, 9.5, 11.0, and 20.0 g; Stoelting Autogenics, Wood Dale, IL), calibrated before every testing session. Each rat was placed in a chamber with a mesh metal floor, covered by an opaque plastic dome. The tested hair was indented five times, at a rate of 2 per second, in the midplantar skin of the hind paw until the hair bowed. If subthreshold, the stimulus intensity was increased by using the next hair. At threshold,

rats responded to one of the five indentations by hind-paw elevation.

Punctate mechanical pain was tested in the same chamber by a single pricking of the midplantar area with a sharpened wooden stick. Duration of hind-paw lifting was recorded using a stopwatch, with a cutoff of 30 s.

Heat pain was tested with the Hargreaves method using radiant heat, emitted from a 150-W lamp, automatically shutting off when the animal withdrew its paw.²¹ Rats were tested in a chamber with a glass floor kept at 32°C. The time lapsed from stimulus onset until hind-paw lifting (“withdrawal threshold”) and the duration of hind-paw lifting until it was placed again on the floor (“response duration”) were recorded, with a cutoff of 30 s. Each hind paw was tested three times, allowing an interval of 2 min between tests to avoid sensitization. Withdrawal threshold and response duration of individual rats were calculated as the average of three trials.

Data Analysis and Statistics

Baseline Sensitivity of Intact Rats. The responses of the left and right intact hind paws to innocuous tactile stimulation, and to noxious heat and mechanical stimuli, were not significantly different. Therefore, for every animal we averaged the data of the two intact hind paws. A grand average was calculated per group. One-way analysis of variance for main effect of diet on the withdrawal threshold to touch was performed using the Kruskal-Wallis test (analysis of variance). Differences in the withdrawal threshold to heat and the response duration to pinprick and heat were assessed using analysis of variance.

Levels of Sensory Disorders in Partial Sciatic Nerve Ligation–injured Rats. Behavioral scores of PSL-injured rats were determined for both hind paws. However, in the current report only the results of the partially denervated hind paw are presented. As reported for the PSL and other neuropathic pain models in rodents, the sensory disorders after nerve injury develop over a few days, reaching a peak and decaying thereafter to normality.² Similar to humans with neuropathic pain, these abnormalities manifest as prolonged response duration (*i.e.*, hyperalgesia) and reduced withdrawal threshold (*i.e.*, allodynia) to a noxious stimulus. We reported previously that averaging the levels of sensory disorders for each animal at postoperative days 3, 8, and 14 provides a reproducible single score expressing the robustness of the pain behavior.¹⁷ The same calculation was used here, and a grand average was calculated per group. $P < 0.05$ was used as the level of significance, corrected when appropriate, using the Bonferroni adjustment. Regression analysis for the effect of preoperative feeding duration with noSOY on the sensory disorders was calculated for all sensory tests.

Results

The baseline sensitivity of intact rats to noxious and innocuous stimuli was not significantly different between groups ($P > 0.5$ for all sensory tests). Therefore, the corresponding data of all groups were pooled. Thus, shifting intact rats from one diet type to another did not affect their baseline sensitivity to noxious and innocuous stimuli. The gray band in figures 1A–D denotes the average (± 1 SEM) baseline sensitivity of intact rats.

After a PSL injury, rats of all groups developed mechanical hyperalgesia. This was expressed as a significantly increased response duration to pinprick compared with the baseline sensitivity (fig. 1D). In contrast, only some of these groups developed an abnormal response to threshold sensory stimulation. This abnormal response manifested as a significant decrease in the withdrawal threshold to tactile and heat stimulation (tactile and heat allodynia, figs. 1A and B, respectively) and a significant increase in the response duration to heat (fig. 1C). The difference in levels of allodynia among these groups depended on the diet.

Effect of Feeding with Soy Diet before versus after Partial Sciatic Nerve Ligation Injury

Comparison “a” in figures 1A–C shows that feeding rats a soy diet before PSL injury significantly attenuated the development of tactile and heat allodynia. Comparison “b” in these figures shows that feeding a soy-free diet before PSL, followed after the nerve injury by a soy diet, did not result in a significant attenuation of tactile and heat allodynia. Therefore, suppression of tactile and heat allodynia after PSL injury occurs only when a soy diet was consumed before nerve injury. Comparison “c” further substantiates this conclusion, since feeding rats a diet devoid of soy before nerve injury was associated with robust tactile and heat allodynia, regardless the diet administered after the injury. Mechanical hyperalgesia to pinprick was not affected by the type of diet consumed before *versus* after PSL injury (fig. 1D).

Duration of Soy Feeding before Nerve Injury versus Levels of Sensory Disorders

The effects on post-PSL neuropathic pain caused by different durations of preoperative noSOY feedings were studied: 14 days (noS14–noS14), 7 days (noS7–noS14), 1 day (noS1–noS14), 15 h (noS15h–noS14), and immediately after surgery (S14–noS14). Regression analysis of the levels of tactile ($r^2 = 0.69$; $P = 0.01$) and heat allodynia (withdrawal threshold [$r^2 = 0.78$; $P = 0.0006$] and response duration [$r^2 = 0.96$; $P = 0.0001$]) and mechanical hyperalgesia ($r^2 = 0.52$; $P = 0.0004$) significantly correlated with log duration of noSOY consumption before nerve injury (figs. 2A–D). The logarithmic regression line of the levels of tactile and heat allodynia, as well as mechanical hyperalgesia, demonstrates that

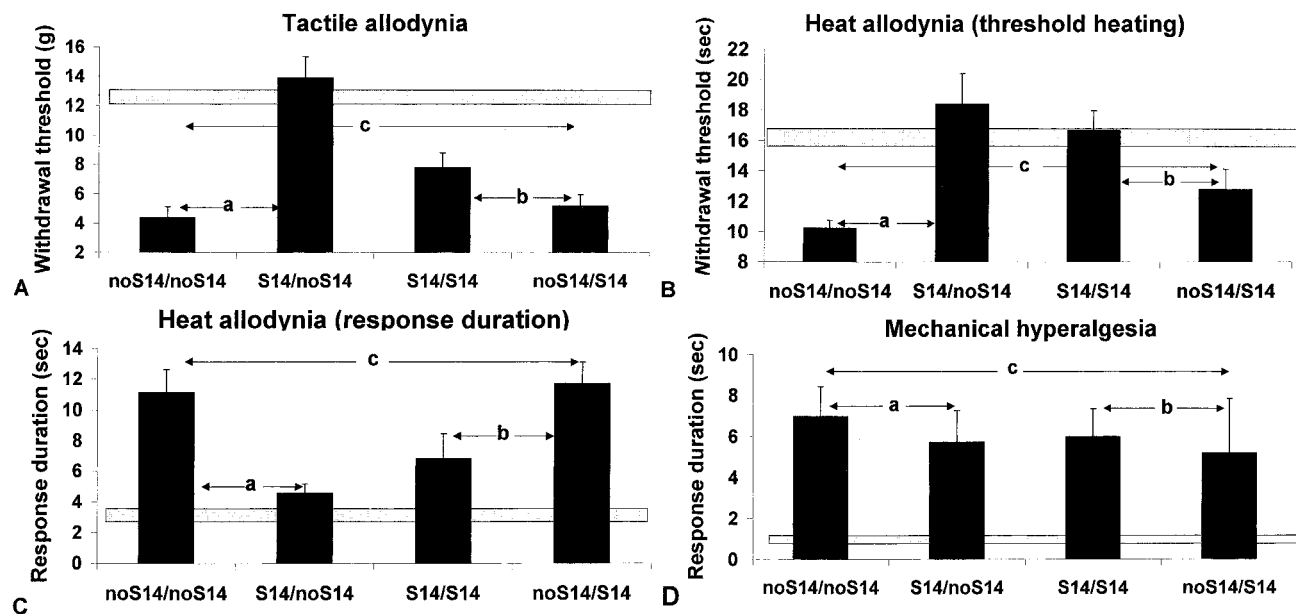


Fig. 1. Average levels (+ SEM bars) of neuropathic pain behavior developing on days 3, 8, and 14 after partial sciatic ligation (PSL) in four groups of rats fed a soy-based diet (SOY; "S") or a diet devoid of soy (noSOY; "noS"). These diets were administered for 14 days before PSL injury and for 14 days thereafter. In the noS14–noS14 group, noSOY was consumed before and after nerve injury; in the S14–noS14 group, SOY was consumed before nerve injury, and noSOY was consumed thereafter; in the S14–S14 group, SOY was consumed before and after nerve injury; in the noS14–S14 group, noSOY was consumed before nerve injury, and SOY was consumed thereafter. The baseline sensitivity of unoperated, intact rats is marked by a gray band delimited by ± 1 SEM across the average. (A) Tactile allodynia. The withdrawal threshold (in grams) to one of five repetitive applications of von Frey hairs to the hind paw at a rate of 2 per second. Comparison a: noS14–noS14 versus S14–noS14, $P < 0.0001$; comparison b: S14–S14 versus noS14–S14, $P < 0.05$; comparison c: noS14–S14 versus noS14–noS14, $P > 0.1$. (B) Heat allodynia. The heating time until paw withdrawal (in seconds). Comparison a: noS14–noS14 versus S14–noS14, $P < 0.006$; comparison b: S14–S14 versus noS14–S14, $P < 0.05$; comparison c: noS14–S14 versus noS14–noS14, $P > 0.1$. (C) Heat allodynia. The duration of paw lifting in response to a threshold noxious heat pulse applied to the plantar surface of the hind paw (in seconds). Comparison a: noS14–noS14 versus S14–noS14, $P < 0.004$; comparison b: S14–S14 versus noS14–S14, $P < 0.04$; comparison c: noS14–S14 versus noS14–noS14, $P > 0.1$. (D) Mechanical hyperalgesia. The response duration (in seconds) to a single pinprick applied to the plantar surface of the partially denervated hind paw. There was no significant difference in the response duration of all four groups ($P > 0.1$, respectively).

discontinuing soy feeding within 15 h preoperatively was sufficient to abolish the suppressive effects of a soy diet on PSL nerve injury.

Discussion

In the current study we sought to investigate which of the two soy-feeding phases (*i.e.*, before *vs.* after nerve injury) lessens the sensory disorders produced by a PSL injury. We found that dietary soy suppressed neuropathic pain only when it was consumed before the nerve injury. Initiation of soy feeding after PSL injury failed to attenuate neuropathic pain. Importantly, dietary soy had a rather short duration of action, as seen when the soy diet was stopped 15 h before PSL. The importance of this finding is twofold. First, it provides a strategy to examine the mechanisms that may be involved in the initiation of the neuropathic pain state. Second, this finding may have clinical applications, as dietary soy may emerge as a preemptive modality to prevent the development neuropathic pain.

This study is the continuation of previous work that used the same rodent PSL model. That study demon-

strated that, when compared with diets devoid of soy protein, ingestion of soy-based diets before and after a PSL injury was associated with significantly lower neuropathic pain-related behavior. Specifically, when rats were fed identical diets differing only in their protein (*e.g.*, soy *vs.* casein), suppressed levels of allodynia and hyperalgesia were associated with consumption of the soy-based diet.^{17–19} Moreover, the exclusion of soy from the diet, rather than the inclusion of casein, has been shown to underlie the development of robust pain behavior after PSL injury.^{17–19} The RMH-1000 diet, which was used here, contained 85% soy protein. It is reasonable to suggest that this protein was the ingredient responsible for suppression of the sensory disorders in the current study as well.

How can a diet consumed preoperatively blunt the development of neuropathic pain? A possible clue to the mechanism by which soy diet may suppress pain relates to its short-term effect, as evidenced by the lack of suppression when the soy diet was stopped as little as 15 h before PSL injury. Because robust neuropathic sensory disorders developed after nerve injury in the groups wherein the soy-containing diet was stopped 15 h or

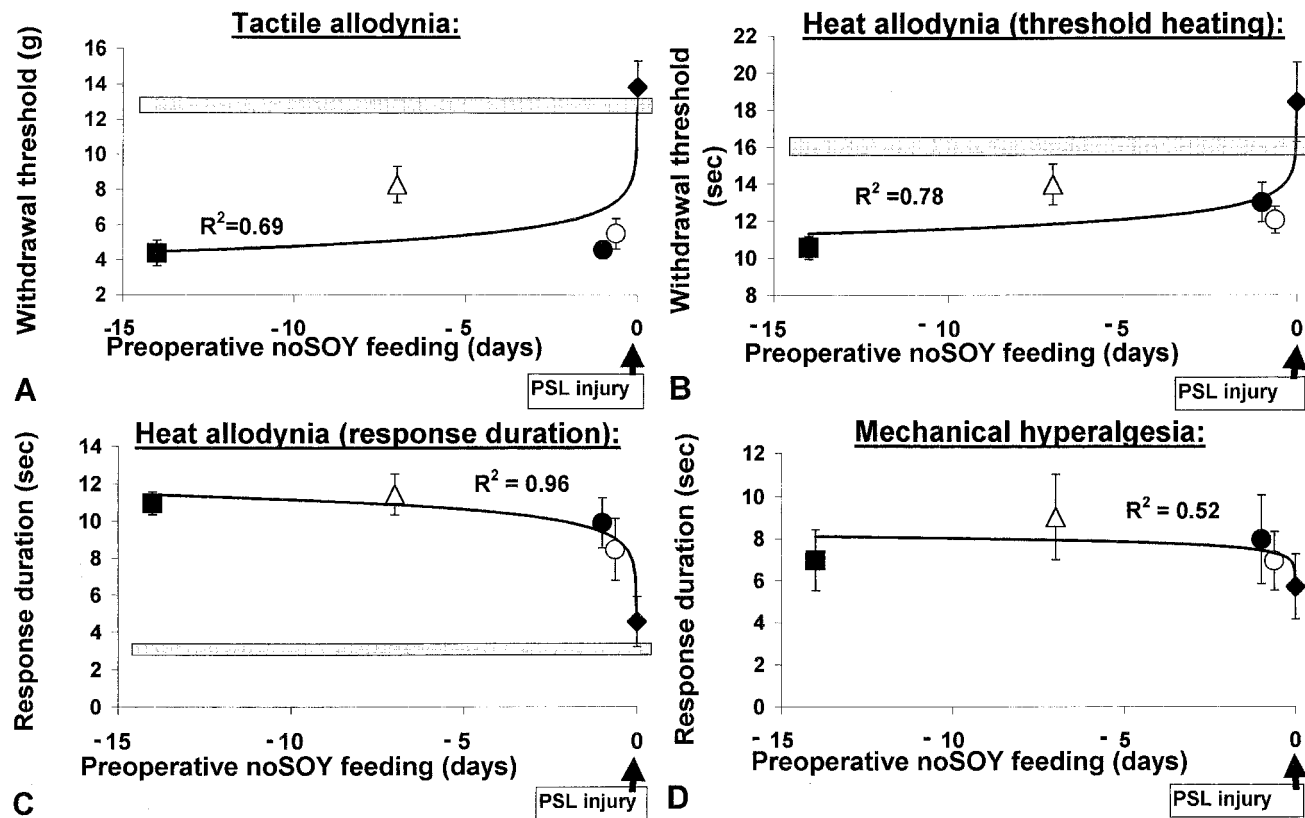


Fig. 2. Neuropathic pain levels (average \pm SEM bars) developing in five rat groups after partial sciatic ligation (PSL) injury. These levels are correlated to the duration (in days) of preoperative noSOY feeding. Compared with linear and exponential regression lines, the data best fitted a log scale. The baseline sensitivity of intact rats is marked by the gray band (average \pm 1 SEM). Rats were switched from a soy-based diet (SOY) to a diet devoid of soy (noSOY) on days 14 (filled square), 7 (open triangle), 1 (filled circle), and 15 h (open circle) before PSL injury (marked by an arrow), or immediately after surgery (filled diamond). Administration of noSOY diet continued postoperatively for 14 days. Levels of tactile allodynia (A), heat allodynia (B and C), and mechanical hyperalgesia (D) significantly correlated with log duration of noSOY consumption before nerve injury. Tactile allodynia: $r^2 = 0.69$, $P = 0.01$; heat allodynia: $r^2 = 0.78$, $P = 0.0006$ (for the withdrawal threshold) and $r^2 = 0.96$, $P = 0.0001$ (for the response duration); mechanical hyperalgesia: $r^2 = 0.52$, $P = 0.0004$.

more before PSL, it is clear that the protective effect of soy diet was transient, terminating before surgery. This is an indication that the washout time for the pain-suppressing moieties in soy was only a few hours. This was further supported by the results showing that when the soy diet was consumed until nerve injury, there was suppression of the neuropathic sensory disorders. In addition, when the soy diet was administered until PSL but not thereafter, the suppressive effect was the same as when the soy diet was continued after PSL. Thus, the soy diet appears to exert its effect only within the very first hours after nerve injury (because of its short washout time). Therefore, we suggest that the processes leading to chronicity of neuropathic pain in the PSL model occur during the first hours after nerve injury. This suggestion is further supported by two observations. First, we noted that the weakened neuropathic pain, when the soy diet was continued throughout the postoperative period, was similar to that recorded when the soy diet was administered until the PSL. Therefore, the presence of dietary soy after the first hours after the PSL injury afforded no additional effect in suppressing

neuropathic pain in this model. Second, substantial pain behavior developed when the soy diet was administered only after nerve injury. It is reasonable to speculate that the amount of food consumed by rats during the first hours after surgery is low. Therefore, the amount of dietary soy in noS14-S14 rats, available for blunting the development of neuropathic pain in the first hours after injury, was likely small.

Previous research identified two early messages registering in the central nervous system that a peripheral nerve injury has occurred. The first message is an electrical barrage of impulses emitted by sensory fibers at the time of nerve damage.²² This injury discharge is emitted by one third to one fourth of all cut sensory axons²³ and lasts seconds up to hours.²⁴ Injury discharge is an important trigger of chronic pain in several animal models of neuropathy.^{25,26} The second message is chemical. During normal conditions, sensory fibers transport neurotrophins, like nerve growth factor, from the periphery to the central nervous system. Neural transport of this message sharply decays within hours after nerve injury. The arrest in nerve growth factor transport has been

associated with central nervous system plasticity after nerve injury and the development of neuropathic pain.²⁷⁻²⁹ After our observation that dietary soy exerts pain suppression within the first few hours after nerve injury, this effect could be mediated *via* one of these two injury messages, or both. That is, dietary soy might reduce injury discharge or its impact on central nervous system neurons. Alternatively, dietary soy may blunt the central nervous system effects caused by arrest of nerve growth factor transport.

Development of neuropathic pain in animals can be preempted by analgesic agents administered before injury. These include suppression of pain behavior in models of acute,^{25,30,31} postoperative³² and chronic pain^{33,34} in rodents, using opioids, *N*-methyl-D-aspartate receptor antagonists, and local anesthetics. The current results add to this list the preemptive administration of dietary soy. The preemptive use of analgesic medications has also been shown to significantly decrease postoperative pain in some, but not all, human experiments.³⁵⁻³⁹ We are not aware of previous studies, either in experimental animals or in humans, showing that the preemptive consumption of specific dietary ingredients before injury decreased postinjury pain. Future clinical trials are required to show whether dietary soy preempts development of neuropathic pain in humans as well.

In the current study, dietary soy was effective in blunting tactile and heat allodynia, but not mechanical hyperalgesia to pinprick. This result suggests that different mechanisms underlie these sensory disorders. This suggestion is supported by previous studies showing that chronic morphine administration enhanced pain-like behavior in response to mechanical, but not thermal, tests.⁴⁰ Moreover, different receptor systems were implicated in thermal hyperalgesia and mechanically evoked pain-related behavior.^{41,42} It is likely that dietary soy is effective in blunting the development of allodynia, but not hyperalgesia, suggesting that this diet operates on processing of input on threshold rather than supra-threshold stimuli.

The active ingredient(s) in soy protein-mediating pain suppression are currently unknown. One candidate group of ingredients are phytoestrogens, compounds abundantly present in soy products. Phytoestrogens inhibit protein kinase C, implicated as an intracellular mediator of the development of neuropathic pain in the PSL model.⁴³ In addition, phytoestrogens possess potent estrogenic activity.⁴⁴ Some, but not all, studies indicate that estrogens show analgesic properties.⁴⁵ We recently found that, at certain plasma concentrations, soy phytoestrogens were associated with suppression of some, but not all, sensory disorders after PSL injury in Wistar rats (unpublished results, June 2001).

In conclusion, dietary soy prevents the development of neuropathic pain behavior only when administered preemptively, before partial nerve injury. For obtaining this

effect, soy diet must be administered until nerve injury. The mechanism of the suppressive effects of soy diets on the development of post-PSL neuropathy needs further elucidation.

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