The effect of acute postoperative pain and chronic neuropathic pain on subsequent weight gain in the rat

Laboratory investigation

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Object. Acute postoperative pain has demonstrated effects on appetite and weight gain in human studies. This study was designed to test the hypothesis that chronic neuropathic pain has a more significant effect on weight than acute postsurgical pain.

Methods. One hundred eighteen rats were separated into 3 groups: common sciatic nerve ligation, surgery without ligation, and no surgery. Each group was further divided to undergo testing at 3, 7, and 14 days. On the day of testing, the rats were tested for signs of pressure and heat hyperalgesia and were weighed.

Results. The effect on the percentage of change in body weight from the day of surgery to the day of testing was statistically significant for both the condition ($F = 15.0$, $p < 0.0001$) and the day of testing ($F = 43.3$, $p < 0.0001$). The rats that received no surgery had a change in weight of 2.3% on Day 3, 4.0% on Day 7, and 10.7% on Day 14. In the nonligation surgery group, the change was −3.8% on Day 3, 2.0% on Day 7, and 9.7% on Day 14. In the ligation surgery group, the change was −6.3% on Day 3, −0.7% on Day 7, and 4.9% on Day 14. This group began gaining weight by Day 14 but continued to have less weight gain than the other groups by Day 14.

Conclusions. Neuropathic pain inhibits weight gain more than normal, postsurgical pain. Recognizing the difference and initiating effective treatment for neuropathic pain may have an impact on the patient’s nutrition.

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Key Words • neuropathic pain • postoperative pain • body weight
Neuropathic pain and body weight

A third group of 40 rats received no surgery. The rats undergoing surgery were allowed to recover for 7 days, during which time the hind paw was heated by a radiant heat source as the rat stood on a clear glass plate. The duration from heat onset to paw withdrawal (in seconds) was recorded. Four measurements were taken at 3-minute intervals such that each paw was tested every 6 minutes, and the 4 measurements were averaged.

Methods

This study was approved by the animal care and use committee at the George Washington University. One hundred eighteen male Sprague-Dawley rats (Harlan) weighing 250–300 g were weighed for a baseline value and separated into the following 3 groups: common sciatic nerve ligation surgery, sham surgery without nerve ligation, and no surgery. The rats undergoing surgery were given 1 mg/kg atropine subcutaneously and anesthetized with 55 mg/kg sodium pentobarbital intraperitoneally. In 45 rats the common sciatic nerve was exposed at the level of the middle thigh by blunt dissection through the biceps femoris. Four loose ligatures of 4-0 chromic gut suture were tied around the nerve in 1-mm intervals as per the protocol of Bennett and Xie.1 The ligatures were tied to constrict the surface of the nerve as seen under a magnification of 40. The incision was then closed with 4-0 nylon sutures using interrupted vertical mattress stitches. Forty-two male Sprague-Dawley rats underwent the same surgical procedure including exposure of the common sciatic nerve, but no ligatures were tied around the sciatic nerve. A third group of 40 rats received no surgery.

The rats were further randomly divided into 3 roughly equal groups representing different durations of the experiment. At 3, 7, or 14 days after the surgery depending on the study group each rat was weighed and tested for signs of pressure and heat hyperalgesia. In the pressure hyperalgesia test, the pressure (in grams) at which limb withdrawal occurred was recorded. Four measurements were taken at 3-minute intervals such that each paw was tested every 6 minutes. These 4 measurements were then averaged. In the heat hyperalgesia test, the plantar surface of the hind paw was heated by a radiant heat source as the

Results

The rats that underwent ligation surgery demonstrated neuropathic pain signs on the paw pinch test (Fig. 1, F = 14.3, p < 0.0001) and on the paw heat test (Fig. 2, F = 34.8, p < 0.0001), whereas the nonligation surgery and unoperated rats did not. The effect on the percentage of change in body weight was statistically significant for surgical condition (Fig. 3, F = 15.0, p < 0.0001) and day of testing (F = 43.3, p < 0.0001). The nonligation surgery group, while exhibiting initial weight loss, gained weight by Day 14 similar to the control group. In the ligation surgery group the change was −6.3% on Day 3, −0.7% on Day 7, and 4.9% on Day 14. This group initially lost more weight than the postoperative pain group. These rats began gaining weight by Day 14 but still lagged behind the other 2 groups. At the end of the study, the animals were anesthetized with sodium pentobarbital intraperitoneally and perfused intracardially with ice-cold 4% paraformaldehyde solution.

Discussion

In this study, pain had a significant impact on weight gain, whether acute or chronic. Whereas unoperated rats had a steady increase in body weight at 3, 7, and 14 days, rats with postoperative pain and those with neuropathic pain initially had a loss of body weight. Given the relatively short duration of the surgeries (10–20 minutes) and the insignificant blood loss, these differences would not be explained by postoperative fluid shifts. Rather, they seem to represent the impact of pain on caloric intake...
and subsequent body growth. At later time points when one would expect the incisional pain to have resolved, the nonligation surgery animals had an accelerated weight gain and eventually had a similar overall weight gain from baseline by Day 14 as the unoperated rats. In contrast, the rats with persistent neuropathic pain eventually started increasing their weight, but never reached the level of weight gain from baseline as their unoperated counterparts within the 14-day study period. This would suggest that the pain, and the persistence or resolution of the pain, impacts the animals’ ability to maintain normal growth patterns.

Pain is known to have a significant impact on a patient’s physiology and psychology. A great deal of study has gone into the impact of postoperative pain on appetite and weight gain because this can influence wound healing and operative success. One study showed that the alleviation of pain with analgesics after laparotomy increased rat weight gain in the postoperative period, suggesting a role of postoperative pain in the inhibition of weight gain. The effects of postoperative pain on weight loss are thought to occur through ileus and appetite suppression produced by inflammatory mediators.

Although chronic neuropathic pain lasts longer than acute pain and can have a greater overall impact on an individual, the influence of chronic neuropathic pain on appetite and weight gain has not been well characterized in animal studies, and it remains unaddressed in objective clinical studies. Investigators have made the reverse comparison, demonstrating that obesity can increase the incidence and severity of chronic pain. In an analysis of self-report measures of depression, patient reports of weight loss were no different in the chronic pain population compared with pain-free patients. A neuroma pain model in the rat inhibited weight gain compared with sham surgery; however, there were potential confounds of this pain model because of its effects on overall rat behaviors (autotomy and decreased activity). The authors of that paper found no correlation between 3 proposed indirect measures of pain in these animals: autotomy, activity level, and body weight. Because this model produces anesthesia in the limb, the investigators could not perform direct tests of pain, such as the pressure and thermal hyperalgesia tests used in the current study. They concluded that they could not definitively assert that any or all of the rats truly developed neuropathic pain.

In the current study, we were able to provide objective signs of neuropathic pain in the animals, including pressure and heat hyperalgesia, to verify that we were assessing true chronic, neuropathic pain. Similar to the current study, the neuroma study showed that the rats with chronic pain eventually started to gain weight but never reached similar weight gain as the sham surgery animals. Both the neuropathic pain rats and the sham-operated rats in the current study lost weight postoperatively compared with the unoperated rats that continued to gain weight consistent with their expected growth. However, by Day 14 the sham-operated rats had achieved similar weight gain to the unoperated rats, but the chronic, neuropathic pain rats remained at a lower weight than the other 2 groups.

Conclusions

These findings suggest that chronic neuropathic pain has a chronic impact on weight gain and body growth, which outlasts that of postoperative acute pain. This could potentially have a long-term effect on overall health. Effective treatment of chronic pain may have a significant impact on many areas of a patient’s health, and monitoring patient weight loss or gain may potentially be an objective method for evaluating efficacy of chronic pain treatment. These findings should be further investigated in human studies to determine the clinical relevance in patients with chronic pain.
Neuropathic pain and body weight

Disclosure

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References


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