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Low barometric pressure aggravates neuropathic pain in guinea pigs

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ABSTRACT

Several clinical studies have demonstrated a consistent relationship between changes in meteorological factors, particularly barometric pressure, and pain intensity in subjects with chronic pain. We have previously demonstrated that exposure to artificially low barometric pressure (LP) intensifies pain-related behaviors in rats with neuropathic pain. In the present study, guinea pigs with unilateral L5 spinal nerve ligation (SNL) were placed in a pressure-controlled chamber and subjected to LP of 10 or 27 hPa below the ambient pressure. The SNL surgery led to increased hindpaw withdrawal frequencies to 34-, 59-, and 239-mN von Frey filaments (VFFs). When the SNL animals were subjected to both LP exposures consecutively, the hindpaw withdrawal frequencies further increased; the effect was most significant when the animals were exposed to LP 27 hPa below ambient pressure. In contrast, no change was seen in a group of sham-operated control animals. These results indicate that fluctuations in LP within the range of natural weather patterns can potentiate neuropathic pain in guinea pigs.

Many studies have demonstrated that patients with chronic pain resulting from conditions such as rheumatoid arthritis, migraine, and neuropathic pain often complain that their condition is aggravated by weather changes [6,7,9,12]. With regard to meteorological factors that may influence pain, a variety of potential contributing factors have been identified, e.g., barometric pressure, humidity, rain, and temperature [6,7,9,12]. In particular, barometric pressure has long been suspected to contribute to changes in chronic pain. For example, the occurrence of migraine attacks was tracked by 77 patients over 2 years, and it was discovered that 13% were sensitive to changes in atmospheric pressure [16].

In a previous study, we demonstrated that artificially lowering barometric pressure (27 hPa decrease over 8 min) augmented pain-related behaviors of rats rendered neuropathic [18,20] or adjuvant inflamed [17]. More recently, we demonstrated that rates of decompression of ≥5 hPa/h and ≥10 hPa/h and magnitudes of decompression ≥5 hPa and ≥10 hPa augmented pain-related behaviors in rats with spinal nerve ligation (SNL) and chronic constriction injury to the sciatic nerve (CCI), respectively [5]. It has been also demonstrated a notable absence of a stimulus–response relationship; that is, the smallest barometric pressure decrease (5 hPa at 5 hPa/h) induced almost the full effect, whereas a more intense pressure decrease (e.g., 10 hPa at 5 hPa/h) induced no further increase in pain-related behaviors in rats [5]. These results indicate that low barometric pressure (LP) exposure that falls within the range of natural weather patterns augments neuropathic pain in rats. We also found that when rats with inner ear lesions in addition to SNL or CCI were exposed to LP, they showed no increase in pain-related behaviors, suggesting that the barometric sensing mechanism influencing how nociceptive behaviors are modulated by LP in rats is located in the inner ear [3].

Our previous research thus raises the possibility that similar mechanisms might contribute to the aggravation of chronic pain in humans during weather changes. However, no concrete evidence exists for LP effects in other species. Therefore the present study aims to demonstrate whether LP-induced aggravation of chronic pain occurs in species other than the rat. We chose the guinea pig as our experimental animal as its hearing and vestibular systems are more similar to those of humans than the vestibular systems of rats, making it an animal model suitable for conducting inner ear experiments [1].

All experiments were conducted with the approval of the Animal Care Committee of Nagoya University and were in accordance with the Fundamental Guidelines for Proper Conduct of Animal Experiments and Related Activities in Academic Research Institutions in Japan. Thirty-two male Hartley guinea pigs with a mean body weight of 250 g (Japan SLC, Hamamatsu, Japan), were used. The animals were housed 2 per cage at a constant temperature (24 °C) with a 12-h light/dark cycle; they had free access to food and water. We attest that all efforts were made to minimize the number of animals used and their suffering.

All surgical procedures were performed under surgically clean conditions and sodium pentobarbital anesthesia (50–60 mg/kg, i.p.). The left L5 spinal nerve was tightly ligated with silk thread,

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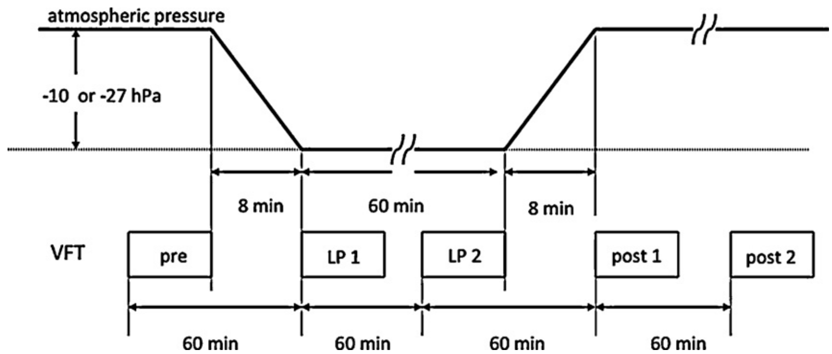

Fig. 1. Time schedule of low barometric pressure (LP) exposures. Behavioral tests (von Frey test; VFT) were carried out 5 times on the day of LP; just before exposure (pre), twice at the lowest pressure [just after (LP 1), and 60 min (LP 2) after reaching the pre-set LP level], and just after (post 1) and 60 min (post 2) after exposure.

according to the method described by Kim and Chung [10], except that only the L5 spinal nerve was ligated in this experiment. The controls were sham-operated guinea pigs, in which the left L5 spinal nerve was exposed but not ligated.

All behavioral tests were performed as blinded comparative studies. Each animal was individually placed beneath an inverted transparent plastic cage (11 cm × 17 cm × 11 cm) with a wire mesh bottom. Pain behaviors induced by mechanical stimulation were measured using homemade von Frey filaments (VFFs, diameter: 0.5 mm, bending forces 34, 59, and 239 mN). Each VFF was applied 10 times (once every 2–3 s) to the plantar surface of the nerve-injured hindpaw, and the number of foot withdrawals was counted. Stimulation of normal human skin with weak (34 and 59 mN) and then the stronger (239 mN) VFFs elicits a sensation of pressure and painful pricking, respectively. A significant increase in the frequency of hindpaw withdrawals in response to these mechanical stimuli was interpreted as punctate hyperalgesia [22,23].

We examined the effects of LP exposure on the SNL-induced pain behaviors in a pressure-controlled chamber, which had been developed and used in our previous studies [5,13]. The barometric pressure of the pressure-controlled chamber was lowered to 10 hPa or 27 hPa below the atmospheric pressure (Fig. 1), which simulates the typical change in pressure observed when a typhoon passes through Japan. This pressure drop was accomplished over 8 min. The pressure was maintained at this level for 60 min and then returned to atmospheric pressure over 8 min. The temperature and humidity were maintained at constant levels (22 ± 2 °C, 50 ± 10%). Behavioral tests were conducted 5 times: just before exposure (pre), twice at the lowered pressure [just after (LP 1) and 60 min (LP 2) after reaching the pre-set low-pressure level], and immediately after (post 1) and 60 min (post 2) after being returned to atmospheric pressure (Fig. 1).

All values are expressed as mean ± standard error of the mean (SEM). Statistical significance was determined by mixed-design two-way repeated measures analysis of variance (ANOVA) for multi-group comparisons, or by one-way repeated measures ANOVA, as appropriate. Tukey's test was used for post hoc comparisons when the *F* value was significant ($p < 0.05$). Kruskal–Wallis and Neuman–Keuls post hoc tests were used to compare the values of experimental groups in the LP-exposure test. Differences were considered statistically significant at $p < 0.05$.

Initial experiments were conducted to obtain a baseline and time course for pain-related behaviors in sham-operated and SNL animals without exposure to LP. Fig. 2 shows the time course of changes in withdrawal frequencies of the left hindpaw of SNL ($n = 9$) and sham-operated ($n = 7$) animals to 34-, 59-, and 239-mN VFFs. Mixed-design two-way repeated measures ANOVA revealed significant effects of both surgery and number of days post surgery on the number of hindpaw lifts [34 mN, surgery: $F_{(1,14)} = 44.5$, day: $F_{(10,140)} = 8.3$, surgery × day: $F_{(10,140)} = 5.1$, $p < 0.001$ for all; 59 mN, surgery: $F_{(1,14)} = 24.8$, day: $F_{(10,140)} = 3.2$, surgery × day: $F_{(10,140)} = 4.8$, $p < 0.001$ for all; 239 mN, surgery: $F_{(1,14)} = 16.1$ ($p < 0.005$), day: $F_{(10,140)} = 3.2$ ($p < 0.001$),

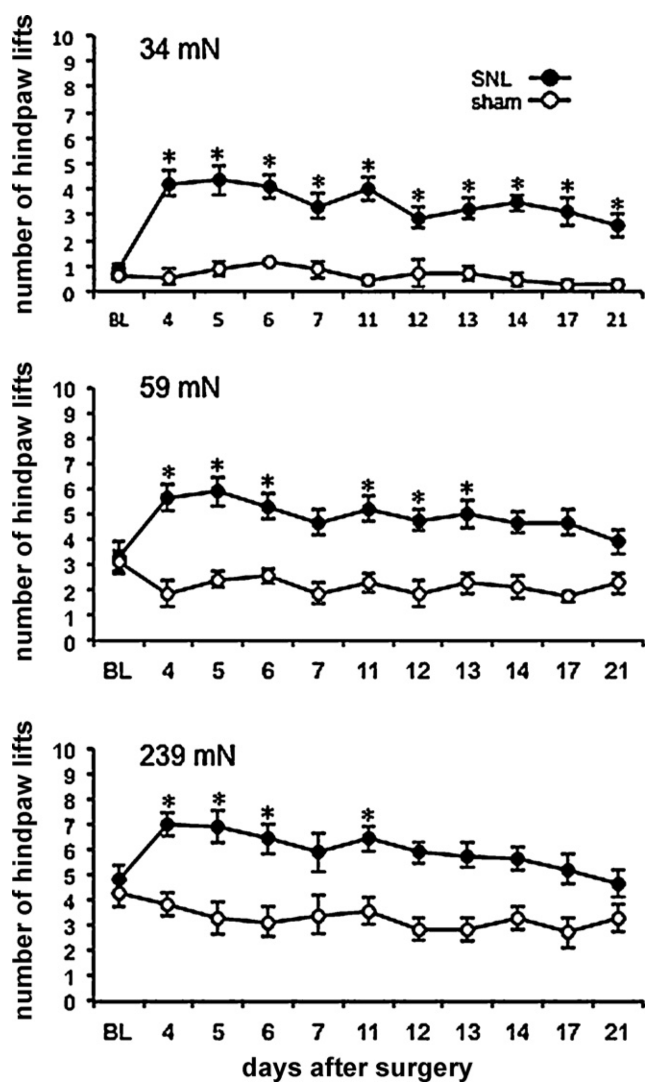

Fig. 2. Time course of changes in punctate hyperalgesia following SNL surgery. The number of hindpaw lifts of SNL ($n = 9$) and sham-operated ($n = 7$) guinea pigs in response to stimulation with 34-, 59-, and 6-mN von Frey filaments (VFFs) are shown (mean ± SEM). The horizontal axis indicates the measurement time points (BL: baseline). *$p < 0.05$ compared with associated baseline values (Tukey's post hoc test).