Paclitaxel is a chemotherapeutic agent that causes peripheral neuropathy as its major dose-limiting side effect. However, the peripheral neuropathy is difficult to manage. A study we recently conducted showed that repetitive administration of aucubin as a prophylactic inhibits paclitaxel-induced mechanical allodynia. However, the mechanisms underlying the anti-allodynic activity of aucubin, which is a major component of Plantaninis Semen, was unclear. In addition to mechanical allodynia, aucubin inhibited spontaneous and mechanical stimuli-induced firing in spinal dorsal horn neurons; however, catalpol, a metabolite of aucubin, did not show these effects. Furthermore, paclitaxel induced the expression of CCAAT/enhancer-binding protein homologous protein, a marker of endoplasmic reticulum (ER) stress, in the sciatic nerve and a Schwann cell line (LY-PPB6 cells); however, this effect was inhibited by aucubin. These results suggest that aucubin inhibits paclitaxel-induced mechanical allodynia through the inhibition of ER stress in peripheral Schwann cells.

Key words  paclitaxel; mechanical allodynia; aucubin; firing; Schwann cell; stress

Goshajinkigan is a traditional herbal formulation that consists of 10 herbal medicines (Rehmanniae Radix, Achyranthis Radix, Corni Fructus, Dioscoreae Rhizoma, Plantaninis Semen, Alismatis Rhizoma, Poria, Moutan Cortex, Cinnamomi Cortex, and Processi Aconiti Radix). It has been shown to attenuate the progression of peripheral neuropathy induced by docetaxel and paclitaxel/carboplatin treatments in cancer patients. However, in spite of its useful anticancer effect, paclitaxel causes peripheral neuropathy, which is characterized by mechanical allodynia, spontaneous pain, shooting and burning pain, tingling, and numbness, with a stocking-and-glove distribution. The peripheral neuropathy is a major dose-limiting side effect, which disturbs cancer treatment with paclitaxel. Therefore, relief of the neuropathy is very important for improving both the QOL and cancer treatment with paclitaxel. Several drugs, including gabapentin and amifostine, have failed to relieve paclitaxel-induced peripheral neuropathy, therefore, alternative therapeutic agents are need.

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administered intraperitoneally (i.p.) to the mice at a dose of 0.1 mL/10 g body weight. The recommended dose of paclitaxel is 210 mg/m² body surface area (package insert of Taxol®; Bristol-Myers Squibb, New York City, NY, U.S.A.), which corresponds to 5.9 mg/kg when the height and body weight are 170 cm and 60 kg, respectively. In in vitro experiments, paclitaxel was dissolved in 100% dimethyl sulfoxide (DMSO), which was diluted in the medium so that the final concentration of DMSO was 1%. Aucubin (Wako Pure Chemical Industries, Ltd., Osaka, Japan: Lot. No. ECM6048) and catalpol (Wako Pure Chemical Industries, Ltd.: Lot. No. ECG0796) were dissolved in physiological saline as well and each solution was injected i.p. at 0.1 mL/10 g body weight. They were administered once daily, starting from 24 h after the paclitaxel injection.

Behavioral Experiments Mechanical allodynia in the hind paws was assessed by punctate stimulation with a von Frey filament (North Coast Medical Inc., Morgan Hill, CA, U.S.A.) at a bending force of 0.69 mN (innocuous stimulation). The responses of the hind paw to the stimulation were scored as follows: 0, no response; 1, lifting of the hind paw; and 2, flinching or licking of the hind paw. The stimulation was applied six times at the same intensity to each hind paw at intervals of several seconds. The average served as the response score.

Electrophysiological Recording The mice were anesthetized with urethane (1.2–1.5 g/kg, i.p.), which produces a long-lasting steady level of anesthesia and does not require the administration of additional doses except in few cases. A thoracolumbar laminectomy was performed to expose the L1–L6 vertebrae, followed by placing the animal in a stereotaxic apparatus. Next, the dura was removed and the arachnoid membrane was cut to create a large window for a tungsten microelectrode. The surface of the spinal cord was irrigated with Krebs solution equilibrated with 95% O2 and 5% CO2 (10–15 mL/min) and containing 117 mM NaCl, 3.6 mM KCl, 2.5 mM CaCl2, 1.2 mM MgCl2, 1.2 mM NaH2PO4, 11 mM glucose, and 25 mM NaHCO3 at 37±1°C. Extracellular single-unit recordings of superficial dorsal horn (lamina I and II) neurons were performed as described previously. Recordings were obtained from the superficial dorsal horn neurons at a depth of 20–150 µm from the surface. These cells were within the superficial dorsal horn and assessed from slices obtained from the same spinal level of same-age mice. Unit signals were acquired with an amplifier (EX1; Dagan Corporation, Minneapolis, MN, U.S.A.). The data were digitized with an analog-to-digital converter (Digidata 1400A; Molecular Devices, Union City, CA, U.S.A.) stored on a personal computer with a data acquisition program ( Clampex software, version 10.2, Molecular Devices) and analyzed with Clampfit software (version 10.2, Molecular Devices). We searched the area on the skin where touch (with a cotton wisp) or noxious pinch (with forceps) stimulus produced a neural response. Mechanical stimulus was applied by skin folding using a fine von Frey filament at a bending force of 0.69 mN. The stimuli were applied for 10 s to the ipsilateral hind limb at the maximal response point of the respective receptive area.

Cell Cultures A Schwann cell line, LY-PPB6, derived from a rat peripheral nerve sheath tumor was provided by RIKEN BRC through the National Bio-Resource Project of the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan. The cells were cultured in Dulbecco’s modified Eagle’s medium (DMEM, Wako Pure Chemical Industries, Ltd.) containing 10% fetal bovine serum in 6-cm petri dishes and used for the experiments at 80–90% confluency. The medium was exchanged to serum-free DMEM supplemented with bovine serum albumin (1%). Next, the cells were pretreated with aucubin for 1 h, followed by the addition of paclitaxel (100 µM) or vehicle (1% DMSO) for 24 h. The cells were then detached and analyzed by Western blotting.

Western Blotting The protein of mouse sciatic nerve or LY-PPB6 cells was extracted using lysis buffer (20 mM Tris–HCl (pH 7.5), 137 mM NaCl, 1% NP-40, 10% glycerol, 1 mM phenylmethylsulfonyl fluoride (PMSE), 10 µg/mL aprotinin, and 1 µg/mL leupeptin), followed by the measurement of protein concentration by the Bradford assay (Bio-Rad, Hercules,
RESULTS

Effects of Repetitive Administrations of Aucubin and Catalpol as Prophylactics on Firing in Superficial Dorsal Horn Neurons in Paclitaxel-Treated Mice

At day 0, PTX (5 mg/kg) or vehicle (VH1) was injected intraperitoneally to male C57BL/6 NCr mice. Next, ACB (50 mg/kg), CTP (50 mg/kg), or vehicle (VH2) was administered once daily as an intraperitoneal injection to the mice, starting from the day after the PTX injection was administered. At day 14, extracellular single-unit recordings were obtained from superficial dorsal horn neurons at a depth of 20–150 μm from the surface. Upper panel: Image is representative of the spontaneous firing in the spinal dorsal horn neurons. Data are presented as mean and standard error of the mean (n=12) (the total number of neurons was 38–61). *Indicates p<0.05 when compared with VH1 plus VH2, whereas † indicates p<0.05 when compared with PTX plus VH2 (Holm–Šidák test).

Catalpol on Paclitaxel-Induced Mechanical Allodynia

A single i.p. injection of paclitaxel (5 mg/kg) induced mechanical allodynia, with a peak effect occurring at day 14 after the injection; however, it almost completely subsided by day 28 (Fig. 1A). The administration of aucubin (50 mg/kg) inhibited exacerbation of paclitaxel-induced mechanical allodynia; however, this effect was not demonstrated by catalpol (50 mg/kg) (Fig. 1B). This result is similar to that obtained in our previous study, in which aucubin and catalpol were administered to mice at doses of 5–50 mg/kg and 50 mg/kg, respectively.13

Effects of Repetitive Administrations of Aucubin and Catalpol on Von Frey Filament-Evoked Firing in Superficial Dorsal Horn Neurons in Paclitaxel-Treated Mice

Spontaneous firing in superficial dorsal horn neurons was significantly increased in mice treated with paclitaxel but not in those treated with the vehicle (Fig. 2). However, this effect was significantly inhibited by the repetitive administration of aucubin (50 mg/kg) (Fig. 2). On the other hand, the catalpol treatment (50 mg/kg) did not affect the spontaneous firing in the neurons (Fig. 2).

The mechanical stimuli induced with the von Frey filament evoked transient firing in the superficial dorsal horn neurons of the vehicle-treated mice after detachment of the filaments from their skins (Fig. 3). However, in the paclitaxel-treated mice, sustained and severe firing in the superficial dorsal horn neurons was induced during application of the mechanical stimuli (Fig. 3). The firing evoked by the mechanical stimuli

CA, U.S.A.). The proteins were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to a polyvinylidene difluoride (PVDF) membrane (Bio-Rad). After blocking with 5% skim milk in Tris-buffered saline containing 0.1% Tween 20 for 1 h, the membrane was incubated with mouse anti-CCAAT/enhancer-binding protein (CHOP) monoclonal antibody (1:2000; Cell Signaling Technology, Danvers, MA, U.S.A.) or rabbit anti-glyceraldehyde 3-phosphate dehydrogenase (GAPDH) polyclonal antibody (1:10000; Novus Biologicals LLC, Littleton, CO, U.S.A.) at 4°C overnight, and then with horseradish peroxidase-conjugated anti-mouse or anti-rabbit immunoglobulin G (IgG) (1:2000; GE Healthcare Bio-Sciences Co., Piscataway, NJ, U.S.A.) for 1 h at room temperature. Signals were visualized by chemiluminescence reaction (GE Healthcare Bio-Sciences Co.) using X-ray films and analyzed using the Imagej program (National Institutes of Health, Bethesda, MD, U.S.A.). Signal intensity was normalized to that of GAPDH.

Statistical Analysis

All the data are presented as the mean and standard error of the mean. Statistical significance was analyzed using one-way ANOVA or two-way repeated measures ANOVA followed by a post hoc Holm–Šidák test (three or more groups). A p value <0.05 was considered statistically significant.

Effects of Repetitive Administrations of Aucubin and Catalpol on Spontaneous Firing in Superficial Dorsal Horn Neurons of Paclitaxel (PTX)-Treated Mice

At day 0, PTX (5 mg/kg) or vehicle (VH1) was injected intraperitoneally to male C57BL/6 NCr mice. Next, ACB (50 mg/kg), CTP (50 mg/kg), or vehicle (VH2) was administered once daily as an intraperitoneal injection to the mice, starting from the day after the PTX injection was administered. At day 14, extracellular single-unit recordings were obtained from superficial dorsal horn neurons at a depth of 20–150 μm from the surface. Upper panel: Image is representative of the spontaneous firing in the spinal dorsal horn neurons. Data are presented as mean and standard error of the mean (n=12) (the total number of neurons was 38–61). *Indicates p<0.05 when compared with VH1 plus VH2, whereas † indicates p<0.05 when compared with PTX plus VH2 (Holm–Šidák test).
Compared to VH1 plus VH2, whereas # indicates expression (Fig. 5).

(50–500 µM) also indicated that pretreatment of the cells with aucubin than that in the vehicle-treated cells (Fig. 5). The results of CHOP in the paclitaxel-treated cells was >30 times higher than that in the sciatic nerves of the vehicle-treated mice (Fig. 4). It was observed that a single injection of paclitaxel resulted in mechanical allodynia, which was of its highest intensity at day 14 after the injection. In our preliminary experiments, a single administration of aucubin did not alleviate paclitaxel-induced allodynia at day 14 after the paclitaxel injection (data not shown), which was similar to the effect observed with goshajinkigan.9) This suggests that aucubin requires repetitive administration to produce an anti-allodynic effect. In addition, the results of the present study show that repetitive administration of aucubin, but not its metabolite catalpol, inhibits the exacerbation of paclitaxel-induced mechanical allodynia, which complements the results in our previous report.10 Therefore, the data suggest that aucubin inhibits the development of mechanical allodynia.

In the present study, we recoded the activity of superficial dorsal horn neurons using the extracellular electrophysiological recording technique. In the paclitaxel-treated mice, firing of superficial dorsal horn neurons was increased by mechanical stimuli in the same way as mechanical allodynia was. Interestingly, spontaneous firing in the superficial dorsal horn neurons was increased in the paclitaxel-treated mice, which suggests that the spontaneous firing may be related to spontaneous pain or numbness. However, the mechanisms underlying the increased activity of superficial dorsal horn neurons in the paclitaxel-treated mice remain unclear. Yadav et al.20) reported that paclitaxel induces the expression of γ-aminobutyric acid (GABA) transporter-1 and increases the uptake of GABA. This results in decreases in GABA levels in the synaptic clefts of spinal dorsal horn neurons. In addition, it has been demonstrated that paclitaxel increases the expression of Na⁺–K⁺–2Cl⁻ cotransporter-1 (NKCC1), which contributes to diminished synaptic inhibition in the spinal cord.21)

**DISCUSSION**

It was observed that a single injection of paclitaxel resulted in mechanical allodynia, which was of its highest intensity at day 14 after the injection. In our preliminary experiments, a single administration of aucubin did not alleviate paclitaxel-induced allodynia at day 14 after the paclitaxel injection (data not shown), which was similar to the effect observed with goshajinkigan.9) This suggests that aucubin requires repetitive administration to produce an anti-allodynic effect. In addition, the results of the present study show that repetitive administration of aucubin, but not its metabolite catalpol, inhibits the exacerbation of paclitaxel-induced mechanical allodynia, which complements the results in our previous report.10 Therefore, the data suggest that aucubin inhibits the development of mechanical allodynia.

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These findings suggest that paclitaxel treatment increases the activity of spinal dorsal horn neurons through the diminishing of synaptic inhibition. Another proposed mechanism is demyelination of sensory neurons, which increases the nerve activity.\(^{14,15}\) Demyelination of sensory neurons leads to the formation of ephapses and sprouting between sensory neurons,\(^{13}\) which suggests that demyelination of sensory neurons may be involved in the induction of abnormal nerve firing that causes neuropathic pain.

In addition to inhibition of mechanical allodynia, the repetitive administration of aucubin, but not catalpol, attenuated both mechanical stimuli-induced and spontaneous firing in the superficial dorsal horn neurons in the paclitaxel-treated mice. These findings suggest that aucubin has effects on both the spinal cord and the peripheral nervous system. Systemic administration of iridoid glycosides containing aucubin has been shown to increase GABA content in the brain.\(^{22}\) Mechanical allodynia is primary mediated by myelinated A-fiber, but not non-myelinated C-fiber, sensory neurons.\(^{46}\) Chanical allodynia is primary mediated by myelinated A-fiber, sensory neurons, which form myelin sheaths\(^{15}\) around the neurons during ER stress.\(^{16,17}\) In the present study, paclitaxel induced the expression of CHOP, an ER stress marker,\(^{19}\) in the sciatic nerves of the mice and in the LY-PPB6 cells; however, this effect was inhibited by aucubin. The comparison of the inhibitory action of aucubin in \textit{in vivo} and \textit{in vitro} studies is difficult. However, the concentration of aucubin (50–500 µM) used in the LY-PPB6 cells may be lower than that in the mouse. In the mouse, a dose of aucubin used was 50 mg/kg of body weight administered by intraperitoneal injection. Since it is considered that the circulating blood volume of mouse is estimated to be 7.3% of the body weight,\(^{24}\) the blood volume is approximately 1.8 mL in mouse (e.g., 25 g of body weight). The concentration of aucubin is approximately 2 mM. Hence, it is considered that these concentrations of aucubin used in \textit{in vitro} study are reasonable. Taken together, these results suggest that aucubin may inhibit demyelination. However, the mechanisms underlying the inhibition of ER stress by aucubin remains unclear. It has been reported that paclitaxel causes ER stress, which results from the stimulation of an increase in intracellular Ca\(^{2+}\) levels by paclitaxel\(^{20}\); however, this is inhibited by aucubin.\(^{25}\) Therefore, aucubin may have protected against paclitaxel-induced ER stress in the mice sciatic nerves and LY-PPB6 cells via inhibition of increase in intracellular Ca\(^{2+}\) levels. It has also been demonstrated that paclitaxel shows cytotoxicity by inducing oxidative stress.\(^{20}\) This indicates that an antioxidiant activity by aucubin\(^{27–29}\) may attenuate paclitaxel-induced cytotoxicity that is mediated through oxidative stress.

In the present study, no changes in the number of peripheral axons were observed in the paclitaxel-treated mice (data not shown), which indicates that a single injection of paclitaxel may not cause severe damage to peripheral neurons. Therefore, we focused on the responses of Schwann cells to the aucubin treatment. However, paclitaxel induces neurotoxicity in neuronal cells by inducing ER stress,\(^{17}\) which suggests that aucubin acts on both Schwann cells and neurons. However, future studies are necessary to investigate the neuronal effects of aucubin on the peripheral nervous system.

It has been demonstrated that repetitive administration of goshajinkigan extract to breast-cancer-bearing mice prevents paclitaxel-induced peripheral neuropathy without interfering with the anti-cancer effect of paclitaxel.\(^{20}\) Therefore, since goshajinkigan contains \textit{Plantaginis Semen}, which contains aucubin as its main component, the clinical use of aucubin may not affect the anti-cancer effect of paclitaxel. However, the effects of aucubin on paclitaxel-induced dysesthesia, cancer-induced pain, and tumors will be evaluated in tumor-bearing mice in future studies.

In conclusion, repetitive administration of aucubin as a prophylactic attenuates the exacerbation of paclitaxel-induced mechanical allodynia and spinal neuronal activation through the inhibition of ER stress.

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\textbf{Conflict of Interest} The authors declare no conflict of interest.

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