[**Original Research**]

Effect of Gosha-Jinki-Gan on Vincristine-Induced Painful Neuropathy in Mice

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Abstract: In the present study, we examined the effect of Gosha-jinki-gan on vincristine-induced thermal hyperalgesia in mice. Mice were intraperitoneally (i.p.) treated with vincristine at a dose of 0.05 mg/kg 1 day after measurement of the pre-drug latency in the tail-flick test, and then treated with a dose of 0.125 mg/kg twice a week for 6 weeks. In vincristine-treated mice, a significant decrease in tail-flick latency developed at 6 weeks after treatment. Pretreatment with Gosha-jinki-gan, at doses of 30, 100 and 300 mg/kg, by peroral administration (p.o.), dose-dependently increased the tail-flick latency in vincristine-treated mice. This significant prolongation of the tail-flick latencies in both vincristine-treated and vehicle-treated mice induced by p.o. Gosha-jinki-gan (300 mg/kg) was dose-dependently and significantly attenuated by i.p. pretreatment with N^G-nitro-L-arginine methyl ester (L-NAME; 2 and 5 mg/kg), a non-specific NO synthase inhibitor. The content of NO metabolites in the spinal cord was significantly less in vincristine-treated mice than in vehicle-treated mice. Pretreatment with Gosha-jinki-gan (300 mg/kg, p.o.) significantly increased the content of spinal NO metabolites in vincristine-treated mice. The present results show that Gosha-jinki-gan can effectively attenuate vincristine-induced thermal hyperalgesia. These results suggest that Gosha-jinki-gan reverses vincristine-induced thermal hyperalgesia through the reversal of vincristine-induced dysfunction of NO/cGMP in the mouse spinal cord.

Key words: Gosha-jinki-gan, vincristine, nitric oxide, hyperalgesia, spinal cord

INTRODUCTION

Several lines of evidence indicate that the vinca alkaloid vincristine, a widely used chemotherapeutic agent, produces painful neuropathy in humans.[1–3] The development of vincristine-induced neuropathy seems to occur in the early stage of vincristine treatment, and the principal symptoms are paresthesias and dysesthesias. The incidence and severity of vincristine-induced painful neuropathy are positively correlated with the duration and doses used, such that with prolonged treatment nearly all patients experience some degree of sensory disturbance or pain. The clinical antineoplastic efficacy of vincristine is limited by the development of dose-dependent sensory neuropathy. If this neuropathy could be prevented, it might be possible to use higher doses of vincristine and thus more effectively treat malignant tumors. Although a variety of remediations have been attempted,[4–8] the lack of information available concerning the mechanisms of vincristine-induced painful neuropathy has hindered the development of treatment strategies.

Recently, we demonstrated that pretreatment with L-arginine (30–300 mg/kg, subcutaneously (s.c.)), a substrate of NO synthase (NOS), dose-dependently reversed vincristine-induced thermal hyperalgesia in mice.[9] The L-arginine-induced increase in tail-flick latencies in vincristine-treated mice was completely antagonized by intrathecal (i.t.) pretreatment with N^G-nitro-L-arginine methyl ester (L-NAME), a non-specific NOS inhibitor.[9] Furthermore, i.t. pretreatment with 8-bromoguanosine 3′,5′-cyclic monophosphate, a membrane-permeable cGMP analog, dose-dependently increased the tail-flick latencies in vincristine-treated mice.[9] The contents of NO metabolites, cGMP and protein levels of neuronal NOS in the spinal cord in vincristine-treated mice were significantly reduced as compared with those in vehicle-treated mice.[9] Based on these results, we proposed that dysfunction of the L-arginine/NO/cGMP cascade in the spinal cord may trigger vincristine-induced thermal hyperalgesia in mice.[9]

Gosha-jinki-gan is a *Kampo* medicine that is composed of 10 crude drugs including processed *Aconiti* tuber, *Cinnamomi* cortex, *Rehmanniae* radix, *Achyranthis* radix, *Corni* fructus, *Alismatis* rhizoma, *Dioscoreae* rhizoma, *Plantaginis* semen, *Hoelen* and *Moutan* cortex. Gosha-jinki-gan has been used since ancient times to treat melosalgia, low back pain and numbness. In recent years, some clinical studies have suggested that Gosha-jinki-gan is especially useful for improving subjective symptoms of diabetic painful neuropathy (e.g., 10, 11). Using animal models of painful diabetic neuropathy, we previously reported that the antinociceptive activity

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of Gosha-jinki-gan was significantly greater in diabetic mice than in non-diabetic mice.[12] Furthermore, since the antinociceptive effect of Gosha-jinki-gan was inhibited by pretreatment with the NOS inhibitor L-NAME, we suggested that the marked Gosha-jinki-gan-induced antinociception in diabetic mice was partly due to NO production.[13] Based on the results of our recent and previous studies, it is possible that Gosha-jinki-gan may reduce the hyperalgesia observed in vincristine-induced painful neuropathy. To examine this possibility, in the present study we investigated the effect of Gosha-jinki-gan on thermal hyperalgesia in vincristine-treated mice.

METHODS

1. Animals

Male ICR mice (Tokyo Laboratory Animals Science, Tokyo, Japan), 4 weeks of age and weighing approximately 20 g at the beginning of the experiments, were used. They were housed at 10 per cage and had free access to food and water. The animal room was maintained at 24±1℃ and 55±5% humidity with a 12-h light-dark cycle (light on at 8:00, light off at 20:00). This study was carried out in accordance with the Guide for the Care and Use of Laboratory Animals as adopted by the Committee on the Care and Use of Laboratory Animals of Hoshi University, which is accredited by the Ministry of Education, Culture, Sports, Science and Technology, Japan.

2. Vincristine treatment

Vincristine sulfate was dissolved in saline to give a stock concentration of 1 mg/ml with a pH between 4.5 and 5.2. The drug was then diluted in saline to a concentration of 5 μg/ml or 12.5 μg/ml, respectively. Mice were intraperitoneally (i.p.) treated with vincristine at a dose of 0.05 mg/kg 1 day after measurement of the pre-drug tail-flick latency, and then treated with a dose of 0.125 mg/kg twice a week for 6 weeks. Control mice received an equal volume of saline. We previously reported that a significant decrease in the tail-flick latency in vincristine-treated mice (compared with that in vehicle-treated mice) was first noted at 4 weeks after the administration of vincristine.[9] Furthermore, significant decreases in the tail-flick latency were also observed at 5 and 6 weeks after the administration of vincristine. Therefore, in the present study, the experiments were conducted 6 weeks after treatment with vincristine or vehicle.

3. Assessment of the nociceptive response

The nociceptive response was evaluated by recording the latency to withdrawal of the tail in response to noxious skin heating. Briefly, the tails of mice were exposed to a focused beam of light from a 50-W projection bulb. The heat intensity was set by adjusting the source voltage of the bulb to 50 V. When a withdrawal response occurred, the stimulus was terminated and the response latency was measured electronically. In the absence of a response up to a predetermined maximum latency (30 s), the trial was terminated to prevent tissue damage. Tail-flick latency was measured before and once a week after the injection of vincristine or vehicle. Mice were given a thermal stimulus only once at each assessment of the nociceptive response. Mice were moved to the testing room at 8:30 to become habituated to the experiment environment, and the experiment was begun at 13:00. Mice were used once at each drug administration.

4. Drugs

Vincristine sulfate and N^G-nitro-L-arginine methyl ester (L-NAME) were purchased from Sigma (St. Louis, MO, U.S.A.). Gosha-jinki-gan was purchased from Tsumura & Co. (Tokyo, Japan) and suspended in 0.5% carboxyl methylcellulose solution. Gosha-jinki-gan was administered peroral (p.o.) 60 min before the testing. A feeding probe was used when drugs and their vehicle were given p.o. L-NAME was dissolved in saline and injected i.p. 30 min before treatment with Gosha-jinki-gan.

5. Measurement of NO metabolites (NO_x)

Mice were killed by decapitation 60 min after the treatment with Gosha-jinki-gan or its vehicle. Spinal cords were quickly removed and immediately homogenized in 6 volumes of methanol. The homogenate was centrifuged at 10,000×g for 10 min at 4℃. The supernatant was used for the analysis of NO metabolites (NO_x). We performed a quantitative analysis of NO_x in the spinal cord by measuring the contents of nitrite (NO_2^-) and nitrate (NO_3^-) with a high-performance liquid chromatography (HPLC)-Griess reaction system (ENO-20, EICOM, Kyoto, Japan). The total level of NO metabolites is the sum of the NO_2^- and NO_3^- levels. The results of the analyses are expressed as pmol/mg tissue.

6. Statistical analysis

The data are expressed as means±S.E.M. In the behavioral experiment, the statistical significance of differences between groups was assessed with Student's t-test (comparison of two groups) or an analysis of variance (ANOVA) followed by the Bonferroni/Dunn test (comparison among multiple groups). In the measurement of NO metabolite contents, the statistical significance of differences between groups was assessed with the Newman-Keuls multiple comparison test.

RESULTS

1. Effects of vincristine on the tail-flick latency in mice

Six weeks after vincristine treatment, a significant decrease in the tail-flick latency compared with that in vehicle-treated mice was observed (vehicle-treated mice, 12.6±0.6 s, vincristine-treated mice, 6.9±0.4 s; $p<0.05$; Fig. 1). No mice showed any sign of motor dysfunction, autotomy, guarding, or body weight loss during chronic treatment with vincristine.

2. Effects of Gosha-jinki-gan on the tail-flick latencies in vincristine-treated mice

The effects of Gosha-jinki-gan on the tail-flick latency in vincristine-treated mice and vehicle-treated mice are shown in Fig. 1. Pretreatment with Gosha-jinki-gan, at

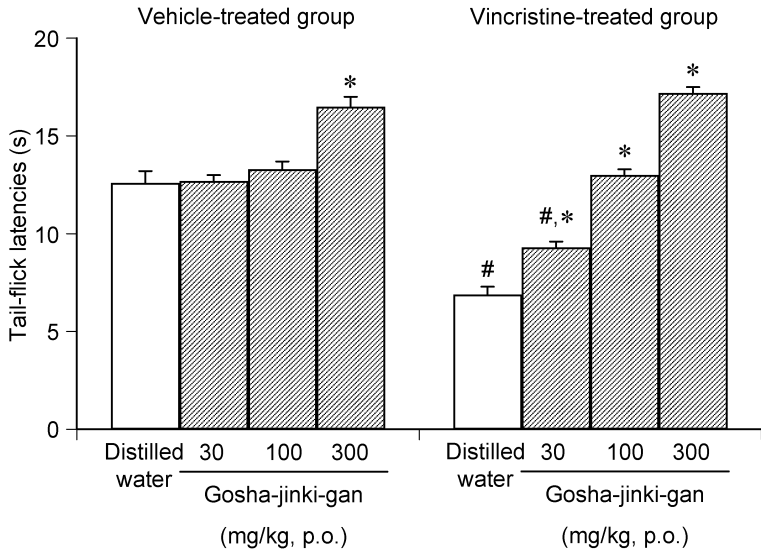

Fig. 1 Effects of Gosha-jinki-gan on the tail-flick latency in vincristine- and vehicle-treated mice. Gosha-jinki-gan was administered p.o. 60 min before testing. The experiments were conducted 6 weeks after the first treatment with vincristine or vehicle. Each column represents the mean with S.E.M. for 9–11 mice in each group. $^{*}p<0.05$ compared with the respective distilled water group (Bonferroni/Dunn test). $^{\#}p<0.05$ compared with the vehicle-treated distilled water group (Bonferroni/Dunn test).

doses of 30–300 mg/kg, p.o., dose-dependently increased the tail-flick latencies in both vincristine- and vehicle-treated mice. Gosha-jinki-gan at doses of 100 and 300 mg/kg significantly increased the tail-flick latency in vincristine-treated mice to the level observed in vehicle-treated mice. Although Gosha-jinki-gan, at doses of 30 and 100 mg/kg, p.o., had no significant effect on the tail-flick latencies in vehicle-treated mice, only a high dose (300 mg/kg) of Gosha-jinki-gan significantly prolonged the tail-flick latency.

3. Effects of L-NAME, a non-specific NOS inhibitor, on the effects of Gosha-jinki-gan on the tail-flick latencies in vincristine-treated mice

The effects of L-NAME, a non-specific NOS inhibitor, on the effects of Gosha-jinki-gan on the tail-flick latencies in vincristine- and vehicle-treated mice are shown in Fig. 2. The significant prolongation of the tail-flick latencies in both vincristine- and vehicle-treated mice induced by p.o. Gosha-jinki-gan (300 mg/kg) was dose-dependently and significantly attenuated by i.p. pretreatment with L-NAME (2 and 5 mg/kg) (vehicle-treated group, $F_{3,34}=11.485$, $p<0.001$; vincristine-treated group, $F_{3,36}=31.35$, $p<0.05$).

4. Effects of Gosha-jinki-gan on the contents of NO metabolites (NO_x) in spinal cord of vincristine-treated mice

The effects of vincristine on the contents of NO metabolites (NO_2^- and NO_3^-) in the mouse spinal cord are shown in Fig. 3. The content of NO metabolites in the spinal cord was significantly less in vincristine-treated mice than in vehicle-treated mice (Fig. 3; $p<0.05$). Pretreatment with Gosha-jinki-gan (300 mg/kg, p.o.) significantly increased the content of NO metabolites in the spinal cord of vincristine-treated mice (Fig. 3; $p<0.05$).

DISCUSSION

Vincristine is well known to impair the motor functions as a result of the peripheral neuropathy.[14] In the present study, we observed no signs of motor impairment and body weight loss during chronic vincrisitne treatment. Same observations have been reported in rats.[15, 16] Our results demonstrated that treatment of mice with vincristine at a dose of 0.05 mg/kg or 0.125 mg/kg twice a week for 6 weeks induced a hypersensitivity to thermal stimuli. The exact mechanism by which vincristine induces sensory dysfunction is not well understood. The potential for vincristine to interact with neuronal microtubules resulting in primary afferent dysfunction has been suggested as one important possible mechanism.[17–19] Indeed, morphological and physiological changes in primary afferent fiber including disorientation of microtubules in a small percentage of C fibers, increased incidence of periaxonal swelling, slowing of conduction velocity in subsets of A and C fibers, and an increased responsiveness of a sub-group of C fibers to mechanical and heat stimulation have all been shown in rats with vincristine-induced hyperalgesia.[19, 20] On the other hand, the direct evidences regarding to the involvement of primary afferent dysfunctions in the development of vincrisitne-induced thermal hyperalgesia were not reported at this time. Several lines of evidence

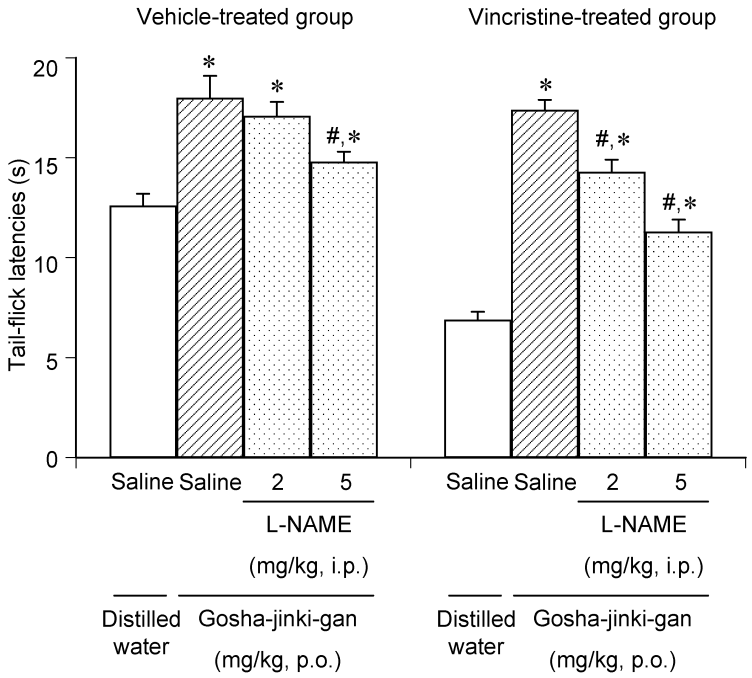

Fig. 2 Effect of N^G-nitro-L-arginine methyl ester (L-NAME) on the effect of Gosha-jinki-gan on tail-flick latencies in vincristine- and vehicle-treated mice. L-NAME or saline was injected i.p. 30 min before p.o. administration of Gosha-jinki-gan or distilled water. The tail-flick test was conducted 60 min after treatment with Gosha-jinki-gan or vehicle. Each column represents the mean with S.E.M. for 8–11 mice in each group. $^*p<0.05$ compared with the respective distilled water-saline-treated group (Bonferroni/Dunn test). $^\#p<0.05$ compared with the respective Gosha-jinki-gan-saline-treated group (Bonferroni/Dunn test).

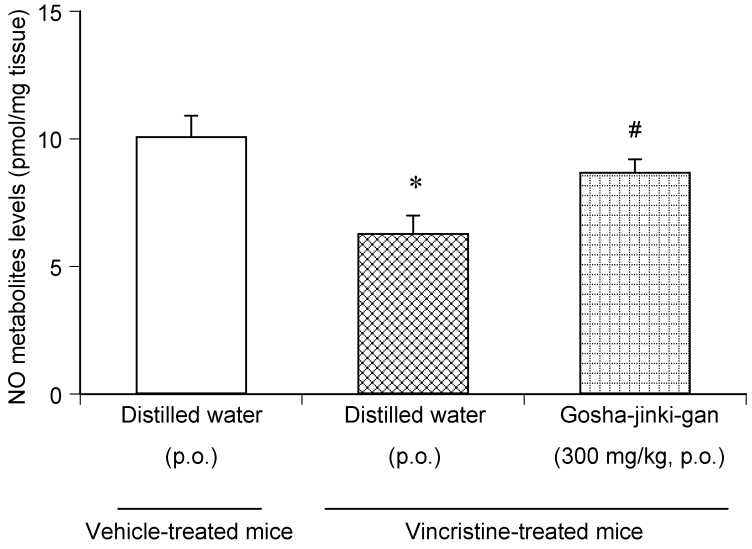

Fig. 3 Effect of Gosha-jinki-gan on the contents of NO metabolites ($NO_2^- + NO_3^-$) in vincristine- and vehicle-treated mouse spinal cord. The experiments were conducted 6 weeks after treatment with vincristine or vehicle. Gosha-jinki-gan was administered p.o. 60 min before the decapitation. NO metabolites were measured using spinal cord taken from each mouse. Each column represents the mean with S.E.M. for 10 samples in each group. $^*p<0.05$ compared with vehicle-treated group (Newman-Keuls test). $^\#p<0.05$ compared with vincristine-treated distilled water group (Newman-Keuls test).

have been suggested that in addition to possible effects on microtubules, the disruption of mitochondrial function and of calcium homeostasis, which produce the activation of many intracellular signaling systems including NOS, might not only participate in but also in fact drive the genesis and maintenance of vincristine-induced hyperalgesia.[21–23]

We demonstrated that Gosha-jinki-gan dose-dependently reversed the decrease in the tail-flick latency in vincristine-treated mice. Indeed, Gosha-jinki-gan at doses of 100 and 300 mg/kg, p.o., reversed the tail-flick latency in vincristine-treated mice to the level observed in vehicle-treated mice. Recently, we demonstrated that either s.c. or i.t. pretreatment with L-arginine, a NO precursor, reversed the decrease in the tail-flick latency in vincristine-treated mice to the level observed in vehicle-treated mice.[9] Furthermore, we suggested that repeated treatment with vincristine may cause the dysfunction of NO/cGMP in the mouse spinal cord, and this may contribute to the pathogenesis of vincristine-induced hyperalgesia.[9] These results lead to the possibility that decreased NO production may produce thermal hyperalgesia, and this effect could be reversed by Gosha-jinki-gan. Indeed, pretreatment with Gosha-jinki-gan (300 mg/kg, p.o.) significantly increased the content of NO metabolites in vincristine-treated mice to the level observed in vehicle-treated mice. These results suggested that Gosha-jinki-gan reverses vincristine-induced thermal hyperalgesia through the reversal of vincristine-induced dysfunction of NO/cGMP in the mouse spinal cord.

Interestingly, the treatment with Gosha-jinki-gan at higher dose of 300 mg/kg, p.o., was prolonged tail-flick latency in vincristine- and vehicle-treated mice, indicating Gosha-jinki-gan produces antinociceptive effect. This result is consisted with our previous indication in non-diabetic and diabetic mice.[13] Moreover, in the present study, we observed that the antinociceptive effect of Gosha-jinki-gan was partly reversed by i.p. pretreatment with a non-specific NOS inhibitor L-NAME in both vincristine- and vehicle-treated mice. This result is consisted with previous our report indicating that the antinociceptive effect of Gosha-jinki-gan was mediated by the increased production of NO in peripheral tissue in diabetic rats.[13] In the light of these results, the antinociceptive effect of Gosha-jinki-gan may be partly mediated by the production of NO in peripheral tissue. In contrast to diabetic mice, we have also reported that the antinociceptive effect of Gosha-jinki-gan in non-diabetic mice was not mediated by the increased production of peripheral NO.[13] Our present results in vehicle-treated mice seem to be contrasted with our previous results in non-diabetic mice. We recently indicated that intrathecal injection of L-arginine, a NO donor, produced antinociception, suggesting that increase of NO production in the spinal cord attenuated nociceptive transmission.[9] Since spinal NO production may be involved in the Gosha-jinki-gan-induced antinociception in normal state, it is possible that intraplantar administration of L-NAME did not show any influence for its antinociceptive effect.[13] These results, therefore, let us to speculate that the Gosha-jinki-gan-induced antinociception may be mediated by the increased production of NO in the spinal cord.

The antinociceptive effect of Gosha-jinki-gan persisted after i.p. treatment with L-NAME in vincristine- and vehicle-treated mice. We have previously reported that intrathecal pretreatment with anti-dynorphin A^{1-13} antiserum or s.c. pretreatment with nor-binaltorphimine, a κ-opioid recetpro antagonist, attenuated the antinociceptive effect of Gosha-jinki-gan, indicating endogenous κ-opioidergic systems in the spinal cord may be involved in the antinociceptive effect of Gosha-jinki-gan.[12] Taken together, these results suggest that the persisted antinociceptive effect of higher dose of Gosha-jinki-gan under the inhibition of NOS activity may be mediated by the activation of endogenous κ-opioidergic systems in the spinal cord.

We must clarify how vincristine-induced dysfunction of NO/cGMP causes a neuropathic pain. The tetrodotoxin-resistant sodium channel is predominantly expressed in capsaicin-sensitive small neurons of the dorsal root ganglion and appears to play an important role in nociceptive transmission,[24–29] and especially in allodynia and hyperalgesia.[30] Consistent with a relationship between NO and sodium channels, Li et al. showed that endogenous NO as well as exogenously added NO donors can inhibit tetrodotoxin-sensitive and tetrodotoxin-resistant sodium currents in baroreceptor neurons.[31] Furthermore, Renganathan et al. reported that the inhibition of endogenous NOS increased both tetrodotoxin-sensitive and tetrodotoxin-resistant voltage-gated sodium currents in small DRG neurons in axotomized rats.[32] Thus, it is possible that the reduction of NO contents in the spinal cord may enhance nociceptive transmission in which tetrodotoxin-resistant sodium channels may play an important role. We previously observed that the duration of the nociceptive behavioral response induced by fenvalerate, a tetrodotoxin-resistant sodium channel activator, was significantly increased by pretreatment with the NOS inhibitor L-NAME and this enhancement was completely abolished by pretreatment with the NO donor L-arginine.[33] Thus, it is possible that vincristine reduces NO contents in the spinal cord and subsequently enhances tetrodotoxin-resistant sodium channels, which could induce neuropathic pain. Therefore, it seems likely that Gosha-jinki-gan reverses vincristine-induced thermal hyperalgesia through the blockade of enhanced nociceptive transmission, in which tetrodotoxin-resistant sodium channels play an important role, as a consequence enhanced of NO production.

In conclusion, the present results demonstrate that systemic Gosha-jinki-gan can effectively attenuate vincristine-induced thermal hyperalgesia. In addition, the blockade of tetrodotoxin-resistant sodium channel-involving nociceptive transmission, which is enhanced by the dysfunction of NO/cGMP, may participate in the

antinociceptive effect of Gosha-jinki-gan on vincristine-induced thermal hyperalgesia. Taken together, these results suggest that Gosha-jinki-gan may be clinically useful for the treatment of neuropathic pain caused by vincristine therapy.

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