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The development of a novel antioxidant-based antiemetic drug to improve quality of life during anticancer therapy

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ABSTRACT

Anticancer agents can effectively treat several types of cancers but are often limited in clinical settings due to various adverse effects. In particular, nausea and vomiting are serious side effects that markedly reduce the patients' quality of life. Accordingly, the development of novel antiemetic drugs that lack side effects is crucial, given that most conventional antiemetic drugs are known to possess side effects. In addition, reactive oxygen species generated by anticancer agents are involved in nausea and vomiting; hence, appropriate antioxidants might also be effective toward nausea and vomiting.

Silicon (Si)-based agents can abundantly generate antioxidant hydrogen in the intestine. Therefore, we assessed whether Si-based agents could be effective against nausea associated with anticancer agents in cisplatin-injected mice. We observed numerous neurons expressing c-Fos protein, a neuronal activity marker, in the nausea-associated regions of the dorsal medulla (area postrema, nuclei of the solitary tract, and dorsal vagal nuclei) 24 h after cisplatin injection. Conversely, mice fed a diet containing 2.5% Si-based agents showed a reduction in c-Fos-positive neurons.

These findings revealed that the Si-based agent alleviated cisplatin-induced nausea. Si-based agents demonstrate potent antioxidant effects by producing hydrogen, which has no known side effects and will be a safer antiemetic agent and greatly help improve the quality of life of patients undergoing anticancer drug treatment.

1. Introduction

Cisplatin, a typical anticancer agent, is known to suppress the growth of cancer cells by inhibiting DNA synthesis and can effectively treat several cancers, including ovarian [1], head and neck [2], testicular, and bladder cancer [3]. However, this drug has been associated with numerous side effects such as nausea, vomiting, loss of appetite, general malaise, hair loss, rash, hot flashes, and anemia [4–6]. In particular, cisplatin can potently induce emesis [7], significantly reducing the patient's quality of life [8], and thus resulting in the cessation or deferral of therapy. Therefore, the control of nausea and vomiting in cancer chemotherapy with cisplatin is an especially important issue to improve therapeutic efficacy. Furthermore, cisplatin-induced serotonin and substance P secretion are reportedly involved in nausea and vomiting associated with the administration of this agent. Accordingly, type 3 serotonin receptor (5-HT3R) antagonists, as well as neurokinin 1 receptor antagonists, have been utilized as antiemetics. However, both antagonists are reportedly associated with adverse effects, such as headache, constipation, and anaphylaxis [9–11]. Therefore, it is desirable to develop a novel antiemetic agent devoid of adverse effects.

Cisplatin administration is known to promote the generation of reactive oxygen species (ROS), such as superoxide anions and hydroxyl radicals, by reducing the levels of the antioxidant, reduced glutathione [12–16]. In addition, ROS generation has been associated with side effects of anticancer drugs, including nausea, vomiting, and renal disorders [17–19]. Therefore, appropriate antioxidants may also be effective for treating nausea and vomiting.

Silicone (Si)-based agents generate a large amount of hydrogen in the intestine for more than 24 h [20–22]. Hydrogen can selectively eliminate hydroxyl radicals, which are highly cytotoxic ROS [23]. Reportedly, the administration of hydrogen molecules effectively alleviated

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Abbreviations

Si-based agent	Silicon-based agent
5-HT3R	type 3 serotonin receptor
ROS	reactive oxygen species
AP	area postrema
NST	nuclei of the solitary tract
DVN	dorsal vagal nuclei

symptoms of renal failure associated with anticancer drug administration without inhibiting the function of the anticancer drug [24,25]. Si-based agents are a novel strategy for administering hydrogen. Oral administration of a Si-based agent can prevent the exacerbation of symptoms associated with Parkinson's disease, ulcerative colitis, chronic kidney disease, skin flap ischemia-reperfusion injury and miscarriage caused by mother-to-child transmission [21,22,26,27]. Therefore, we hypothesized that a Si-based agent would also be effective for anticancer drug-induced vomiting.

As rodents (e.g., rats and mice) lack a vomiting reflex, the degree of nausea cannot be directly evaluated [28,29]. Accordingly, we assessed the activity of nuclei involved in nausea as an alternative indicator. In the present study, we investigated whether Si-based agents are effective against cisplatin-induced nausea in mice.

2. Methods

2.1. Animals

All experiments were performed in seven-week-old C57Bl/6J male mice (Japan SLC, Shizuoka, Japan). Animals were housed at 23–25 °C and were provided special rodent pellets and water *ad libitum*. Cisplatin (FUJIFILM Wako Chemicals Corporation, Osaka, Japan) was suspended in saline to prepare a 3 mg/mL solution. Nausea was induced by intraperitoneal administration of 300 μL cisplatin solution. All experimental procedures were approved by the Animal Ethics Committee of Osaka University according to the National Institute of Health Guide for the Care and Use of Laboratory Animals. Efforts were made to minimize the number of experimental animals and to optimize their living conditions.

2.2. Diets

Two special diets (Oriental Yeast Co., Ltd., Tokyo, Japan) were prepared, as previously reported [21]. AIN93 M was used as the control. For the Si-based agent-containing diet, we used AIN93 M containing 2.5% of the Si-based agent. Mice were administered respective diets one week before establishing the emesis model.

2.3. Frozen sample preparation

The day after cisplatin administration, mice were anesthetized using a combination anesthetic solution (0.3 mg/kg medetomidine, 4.0 mg/kg midazolam, and 5.0 mg/kg butorphanol in 0.9% saline) [30], followed by transcardial perfusion using 4% paraformaldehyde in 0.1 M phosphate buffer (PB; pH7.4). Next, the harvested brain and kidneys were postfixed in the above fixing solution at 4 °C overnight, immersed in 30% sucrose in 0.1 M PB at 4 °C, and frozen in dry ice. Then, the prepared brain samples cut into 30-μm-thick sections using a cryostat microtome. Sections were floated in 0.01 M phosphate-buffered saline (PBS) and maintained at 4 °C until use. The harvested kidneys were cut into 20-μm-thick sections, mounted on MAS-coated slides (Matsunami-glass, Osaka, Japan), and stored at −80 °C until use.

2.4. Immunofluorescence staining

Immunofluorescence staining using free-floating sections was performed as described previously [31]. In brief, free-floating brain sections were incubated with 0.01 M PBS containing 0.3% Triton-X and 3% bovine serum albumin for 30 min to increase antibody permeability and inhibit non-specific staining. Subsequently, sections were treated with anti-*c*-Fos rabbit polyclonal antibodies (1:1000; Catalog No. ab190289; Abcam) in a blocking buffer at 4 °C overnight. After washing thoroughly, the sections were incubated with Alexa 568 conjugated anti-rabbit IgG antibody (1:500; Catalog no. A-10042; Thermo Fisher Scientific) in 0.01 M PBS for 1 h. Then, sections were washed several times in 0.01 M PBS and subsequently mounted on slides using PermaFluor (Thermo Fisher Scientific). The stained samples were analyzed using a BX53 microscope (Olympus Corporation, Tokyo, Japan).

2.5. Evaluation of immunofluorescence signals and statistical analysis

In brief, c-Fos positive cells were enumerated in nuclei associated with nausea and vomiting (AP, area postrema; NST, nuclei of the solitary tract; DVN, dorsal vagal nuclei). The number of active cells in each group was defined as the average number of cells in eight mice. Data are expressed as the mean ± standard error of the mean (SEM). The results of the Student's *t*-test were considered significant at $p < 0.01$, versus the control group.

2.6. Hematoxylin and eosin (HE) staining

Briefly, kidney samples were stained with HE solution (FUJIFILM Wako Chemicals Corporation). After dehydration using a series of ethanol solutions, samples were sealed with Entellan (Merck KGaA, Darmstadt, Germany) using xylene. Finally, all samples were analyzed using a BX53 microscope (Olympus Corporation).

3. Results

Herein, we investigated whether our Si-based agent can effectively mitigate nausea associated with anticancer drug therapy using mice administered cisplatin intraperitoneally. As mice lack the ability to vomit, the degree of nausea was evaluated by analyzing the activity of representative medullary nuclei involved in nausea (input: AP and NST; output: DVN). One week before cisplatin administration, mice were provided a diet containing 2.5% of the Si-based agent (Si group) or a diet lacking the Si-based agent (control group). On immunostaining for c-fos, a neuronal activity marker, numerous c-fos positive cells were observed in the nuclei of AP, NST, and DMV in the control group (Fig. 1B). However, these positive cells were not observed in the dorsal medulla of mice intraperitoneally administered saline instead of cisplatin (Fig. 1A). These findings confirmed that cisplatin administration activated the positive cells. Conversely, the number of positive cells in the AP, NST, and DMV was significantly reduced in the Si group when compared with the control group (Figs. 1C, 2A and 2B).

In contrast, acute nephropathy can also induce nausea and vomiting. Hence, we next confirmed that nausea observed in the present study was a symptom associated with cisplatin administration. Accordingly, we performed HE staining to determine whether the cisplatin concentration used in the study could induce renal structural abnormalities. Renal damage associated with cisplatin administration is an abnormality observed in the proximal renal tubule [32]. However, no apparent structural abnormalities were detected in the proximal tubule of either group (Fig. 3A-F). In addition, no apparent abnormalities were noted in the renal cortex, including the distal tubules, glomeruli, and renal medulla (Fig. 3A-F).

Collectively, these findings revealed that administration of the Si-based agent could alleviate symptoms of nausea associated with cisplatin administration.

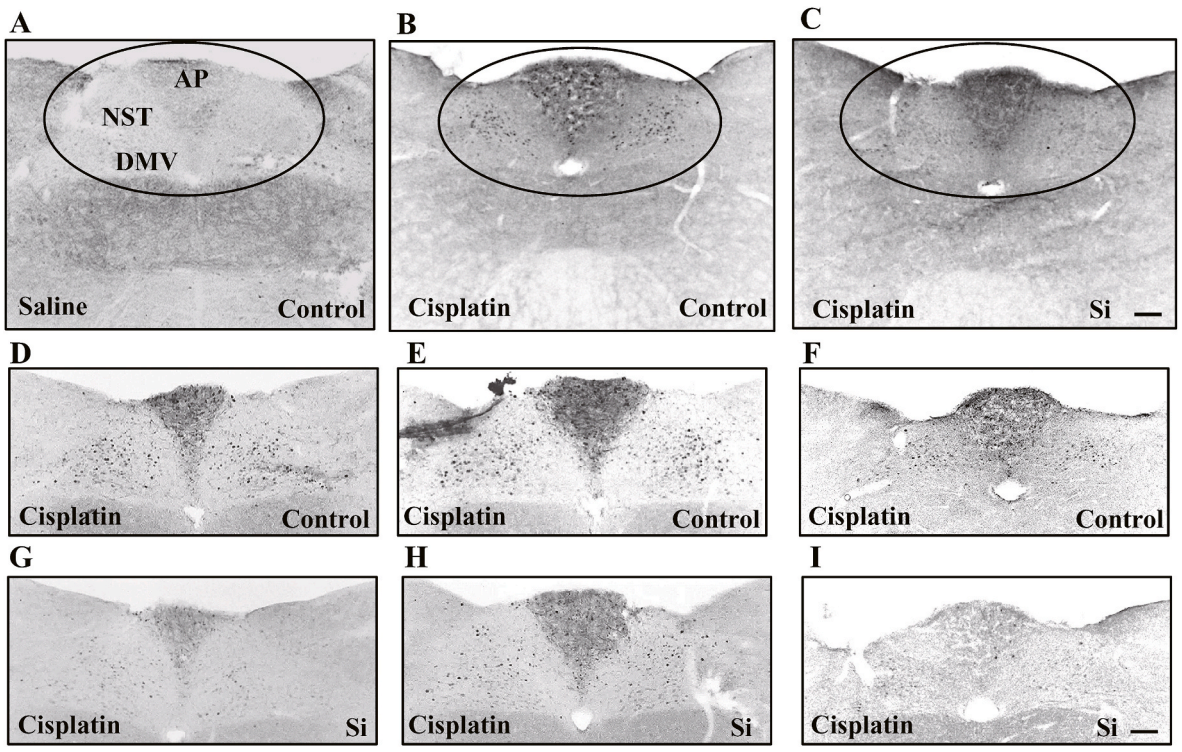

Fig. 1. Morphological analysis of the neuronal activity in the dorsal medulla involved in nausea, using immunostaining for c-Fos. (A, B, C) Representative microphotographs of the dorsal medulla involved in nausea in the saline-injected group (A), the control group (B), and the Si-based agent group (C). Circles indicate the region of interest. (D–I) Additional photographs of the control group (D–F) and Si-based agent group (G–I). Scale bar: 100 μm. AP, area postrema; NST, nuclei of the solitary tract; DMV, dorsal vagal nuclei.

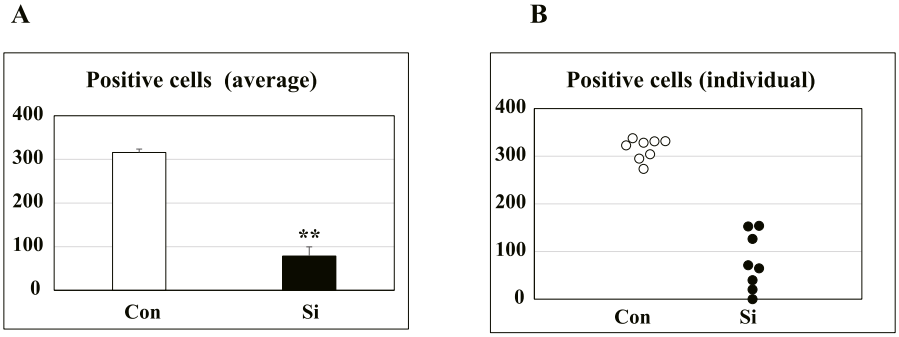

Fig. 2. The number of c-fos positive cells in the dorsal medulla. The bar graph indicates mean values (D). The dot graph indicates individual values (E). White: Control group. Black: Si-based agent group. Data are expressed as mean ± standard error of the mean (SEM) of eight mice per group. $^{**}p < 0.01$ *vs.* control group, determined by Student's paired *t*-test.

4. Discussion

It is well-known that rodents such as rats and mice cannot vomit. Therefore, the consumption of a non-nutritive substance (e.g., kaolin), namely pica behavior, has been established as a method for evaluating rodent nausea [24,25]. Conversely, cisplatin-induced vomiting and nausea stimulate the small intestine and brain vomiting center, resulting in the vomiting reflex via serotonin and substance P secretion. In addition, neural activation of the AP and NST in rodents is shown to be directly proportional to pica behavior under vomit-inducing conditions [33,34]. Furthermore, according to a study using experimental animals (e.g., cats, ferrets), known to possess a vomiting reflex, cisplatin injection reportedly increased c-Fos expression in the AP and NST [35–37]. Therefore, we used the activation of typical nerve nuclei involved in vomiting signals to indicate nausea in mice. Accordingly, we examined the AP and NST, the central input areas of the vomiting stimulus, and the DMV, known to be involved in the output. In the present study, the neural activity of nausea-involved nuclei was significantly suppressed in the Si group when compared with the control group. Thus, Si-based agents might effectively suppress nausea, a well-known side effect of cisplatin therapy.

Cisplatin also has a high affinity for sulfhydryl (SH) groups [26]. The interaction of cisplatin with the SH group causes the depletion of reduced glutathione, which suppresses the capacity of the cellular antioxidant system, resulting in the subsequent accumulation of ROS or oxides [12,13,38]. Notably, ROS generation during anticancer treatment promotes immune enhancement for tumor cell removal [39,40]; however, oxidative stress caused by abundant ROS is strongly associated with the induction of nausea and vomiting following cisplatin administration. Accumulated evidence suggests that oxidative stress is one

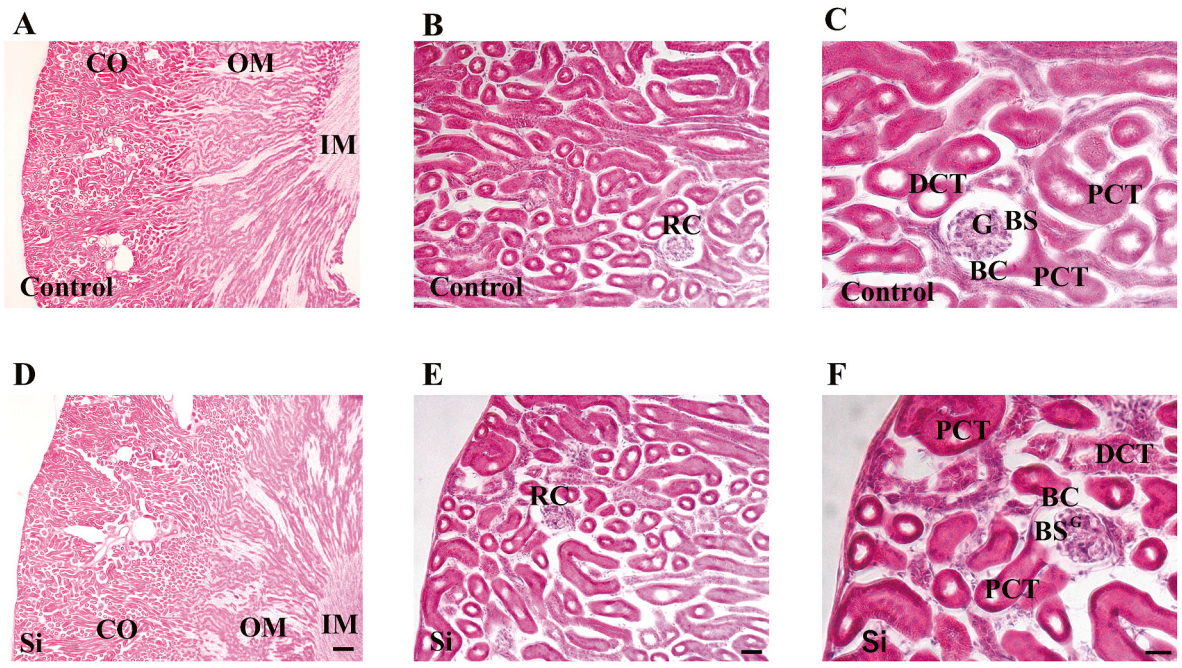

Fig. 3. Morphological analysis of the kidney using hematoxylin-eosin (HE) stain. (A–F) The representative HE-stained image of the kidney for the control group (A–C) and Si-based agent group (D–F). Overview of the kidney (A, D), high magnification of renal cortex (B, E) and renal corpuscle (C, F). CO: renal cortex. Scale bar: 200 μm (A, D); 20 μm (B. E); 50 μm (C, F). OM, renal outer medulla; IM, renal inter medulla; RC, renal corpuscle; G, glomerulus; BC, Bowman's capsule; BS, Bowman's space; PCT, proximal convoluted tubule; DCT, distal convoluted tubule.

underlying mechanism that induces vomiting following chemotherapy with agents such as cisplatin [41,42]. Cisplatin induces lipid peroxidation in the brain, liver, and small intestine and releases serotonin by generating free radicals. Moreover, ROS generated by the active cisplatin metabolite can stimulate enterochromaffin cells in the small intestine to release serotonin. Serotonin reportedly stimulates 5-HT3R in vagal afferents, inducing the vomiting reflex in the brainstem [41,42]. As ROS are involved in cisplatin-induced vomiting, administration of an antioxidant capable of detoxifying ROS could afford relief. Several studies have reported that various antioxidants, such as vitamin C and vitamin E, significantly contribute to antiemetic effects [43–45]. Notably, antioxidants eliminate generated free radicals and protect enterochromaffin cells from oxidative damage, thereby suppressing the release of serotonin in the vomiting pathway [46]. Accordingly, antioxidants can reduce not only oxidative stress associated with chemotherapy but also the occurrence of side effects [18,40]. However, ROS, such as low concentrations of superoxide and hydrogen peroxide, act as signaling molecules and regulate apoptosis, cell proliferation, and cell differentiation [47]. As these antioxidants also eliminate important ROS possessing physiological functions, excessive antioxidant intake might cause adverse effects, including a lowered immunity. Recent studies have indicated that excess amounts of antioxidants block essential defense mechanisms in the body, thus increasing mortality and cancer incidence [48–50]. Therefore, antioxidants that can selectively remove harmful active oxygen are required.

Hydrogen act as antioxidants by selectively eliminating harmful ROS, such as hydroxyl radicals [23]. Unlike other antioxidants, if a large amount of hydrogen molecules is ingested, the excess is excreted from the living body, given the excellent permeability of hydrogen molecules. Therefore, hydrogen molecules may be more beneficial antioxidants than other antioxidants, as quantitative accuracy is not critical. Our Si-based agent reacted with water to continuously generate abundant hydrogen. With increasing pH, more hydrogen is generated, and it was to constantly fill the intestinal tract with hydrogen by oral administration [22]. Hydrogen is efficiently absorbed in the intestine and reduces lipid peroxide, which are highly cytotoxic [22]. On the other hands, since the anticancer effect of anticancer drugs is mediated by oxidative stress induced by ROS, administration of antioxidants may attenuate the effect [51].

However, it has been reported that the antioxidants cimetidine and hydrogen do not attenuate the action of cisplatin [24,52]. Hence, hydrogen molecules do not reduce the anticancer effects of chemotherapy. Currently, reports on side effects associated with hydrogen administration are unavailable, and hence, they appear extremely effective as antiemetic agents in anticancer drug therapy. Since the Si-based agent can be considered an excellent hydrogen for *in vivo* administration, the Si-based agent was proven to alleviate nausea and vomiting by eliminating ROS generated by cisplatin and its active metabolites (Fig. 4). In conclusion, a Si-based agent could substantially improve the quality of life of patients with cancer receiving chemotherapy. In addition, administration of antioxidants alleviated oxidative stress-induced side effects (hepatotoxicity) associated with schizophrenia therapeutics [53]. In the future, Si-based agent could be effective drugs to protect patients from side effects associated with effective therapies.

Author contributions

H·Y and Y.K. designed the study, performed experiments, analyzed the data, and wrote the paper. Y.K. and H.K. developed the method for fabrication of Si-based agent. S.S. supervised this study and provided intellectual directions. All authors discussed the findings and commented on this manuscript.

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Disclosure of interest

The authors report no conflict of interest.

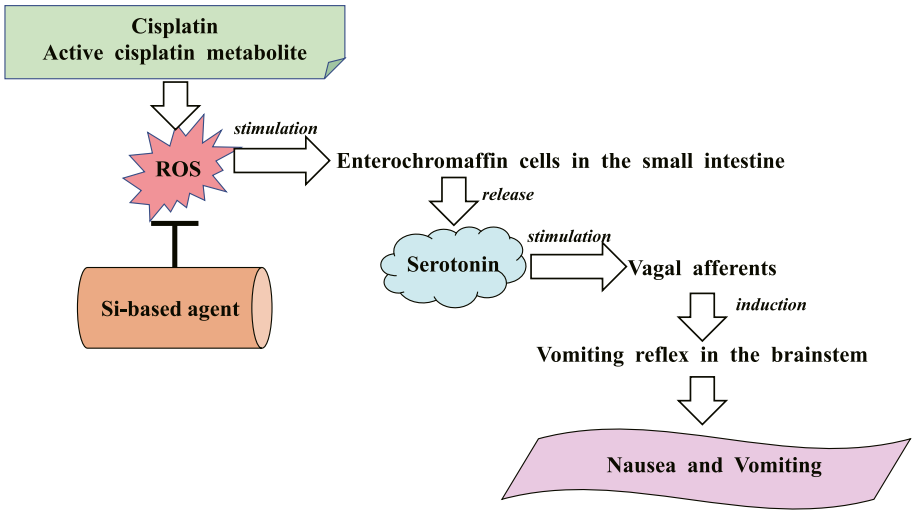

Fig. 4. The hypothetical pathways of cisplatin-induced nausea and vomiting regulated by Si-based agent are illustrated.

Data availability

No data was used for the research described in the article.

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