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Induction and antagonism of pica induced by teriparatide in rats

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ABSTRACT

Intermittent subcutaneous injection of teriparatide, an active fragment of human parathyroid hormone, is clinically used for the treatment of osteoporosis. Patients suffer from nausea, which is one of the side effects teriparatide induces; however, the etiology of teriparatide-induced nausea remains unknown. We have reported pica, kaolin ingestion behavior, can be used as an assessment of nausea-related response in rats. In this study, we investigated the characteristics of teriparatide-induced pica and the abilities of anti-emetic drugs to inhibit teriparatide-induced pica. Male and female adolescent (4-week-old), young (8-week-old), and adult (30-week-old) naive rats, and ovariectomized (OVX: 17-week-old) and sham-operated (17-week-old) rats subcutaneously received teriparatide (0.4 mg/kg, $n=4$), and their kaolin and food intakes were monitored for 24 h after the injection. Among the tested rats, we found that OVX rats, rather than male, female, and sham-operated rats, showed marked teriparatide-induced pica (0 mg/kg: 0.17 ± 0.07 g, 0.4 mg/kg: 6.18 ± 0.91 g). Teriparatide-induced pica in OVX rats was inhibited by intraperitoneal pretreatment with serotonin 5-HT_3 (granisetron 0.5 mg/kg), dopamine D_2 (prochlorperazine 0.5 mg/kg), neurokinin NK_1 (fosaprepitant 1 mg/kg), and histamine H_1 (diphenhydramine 10 mg/kg) receptor antagonists to 70%, 11%, 19%, and 59% of that in vehicle-treated control, respectively. These results suggest that teriparatide-induced pica in OVX rats has the potential to reflect teriparatide-induced nausea; 5-HT_3, D_2, NK_1, and H_1 receptor activation is involved in the development of this behavior; antagonists of these receptors have the potential to be medical candidates used as treatments for teriparatide-induced nausea in human patients.

1. Introduction

Osteoporosis is considered a serious public health problem, and it is estimated that over 200 million people worldwide suffer from it. This disease is characterized by a reduction in bone mineral density (BMD) and deterioration of the bone microarchitecture, leading to an increased risk of bone fracture of the hip, wrist, and spine (NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001). It is known that menopause increases the risk of developing osteoporosis. In fact, the incidence of osteoporosis in women aged 50 and over is several times higher than that of younger women and men (Hamdy, 2010).

Treatment for osteoporosis is mainly based on (1) preventing and slowing BMD reduction with medication, such as bisphosphonates and denosumab, (2) inducing absorption of calcium, by using calcium supplements and vitamin D, and (3) hormone replacement therapy with estrogen, progesterone, and calcitonin (Eriksen et al., 2013; Riek et al., 2011). Parathyroid hormone (PTH), a hormone secreted from the parathyroid gland, is involved in the release of calcium from bones and the enhancement of calcium reabsorption in the kidney to increase the serum calcium level (Boden and Kaplan, 1990). However, some reports have described that intermittent administration of PTH and its active fragment, teriparatide (human PTH(1–34)), has the potential to increase BMD and to improve the skeletal microarchitecture; therefore, teriparatide is an approved anabolic medication that reduces the incidence of osteoporotic fractures (Hodsman et al., 2005; Miyauchi et al., 2010; Nakamura et al., 2012; Sugimoto et al., 2014).

In clinical practice, daily teriparatide injection of 20 μg (Forteo®) and once-weekly teriparatide injection at a dose of 56.5 μg (Teribone™) are currently available. One of the most

Abbreviations: BMD, bone mineral density; CTZ, chemoreceptor trigger zone; OVX, ovariectomy; PTH, parathyroid hormone (parathormone); RSA, rat serum albumin

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common side effects of teriparatide therapy is nausea (Rizzoli and Reginster, 2011). From a clinical investigation, it was reported that nearly 20% of patients treated with teriparatide suffer from nausea (Brixen et al., 2004; Neer et al., 2001; Nakamura et al., 2012). Osteoporosis is considered as an important factor in the development of teriparatide-induced nausea; however, the precise etiology remains unclear. Nausea is not a life-threatening symptom, but its insufficient control reduces the patient's quality of life and becomes a risk factor for refusal to undergo further therapy.

To identify a treatment and a method of preventing teriparatide-induced nausea in preclinical study, objective evaluation of nausea in experimental animals is required. Nausea is defined as a subjective and unpleasant feeling described as recognition of the need to vomit (Quigley et al., 2001); thus, determination of the severity of nausea is rather difficult. We have reported that pica, a behavior characterized by eating non-nutrient materials, such as charcoal, soil, or clay (kaolin), can be used as an assessment of gastrointestinal discomfort and nausea-related response in rats, because this behavior is induced by several emetic stimuli in humans, and it is inhibited by anti-emetic drugs (Yamamoto et al., 2004, 2007, 2014). In the present study, in order to develop an animal model for the evaluation of teriparatide-induced nausea, we firstly investigated the effect of teriparatide on the development of pica in rats in different age and gender groups, as well as ovariectomized rats. We also investigated the effects of serotonin 5-HT_3, dopamine D_2, neurokinin NK_1, and histamine H_1 receptor antagonists on the teriparatide-induced pica in rats.

2. Materials and methods

2.1. Teriparatide-induced pica in rats

All experiments were approved by the Animal Care Committee of the School of Allied Health Sciences, Faculty of Medicine, Osaka University, and were conducted in accordance with the Animal Experiment Guidelines of Osaka University.

Male and female adolescent (4-week-old, body weight: male 100–120 g; female 70–90 g), young (8-week-old, body weight: male 220–240 g; female 170–190 g), and adult (approximately 30-week-old, body weight: male 350–450 g; female 300–400 g) naive Wistar/ST rats, and young female Wistar/ST rats subjected to bilateral ovariectomy (OVX, body weight 300–330 g) or sham-surgery rats (sham-operated, body weight 250–280 g) were obtained from Japan SLC (Shizuoka, Japan). The surgical procedure of OVX was as follows. Briefly, the animals were anesthetized with butorphanol tartrate (Vetorphale®; Meiji Seika Pharma, Tokyo, Japan, at 2.5 mg/kg, i.p.), medetomidine hydrochloride (Dorbene Vet®; Kyoritsu Seiyaku, Tokyo, Japan, at 0.15 mg/kg, i.p.), and midazolam (Sandoz, Tokyo, Japan, at 2 mg/kg, i.p.). The dorsal surgical area was bilaterally shaved and disinfected. A small skin and muscle incision (approximately 2 cm) was made to access the peritoneal cavity and bilateral uterine ligation was conducted; then, the ovaries were removed via this incision. For sham ovariectomy surgeries, the ovaries without ligation were left in place. The muscle and skin were closed using silk suture. Rats received prednisolone-fradiomycin sulfate spray (Aerozolin®; Takeda Pharmaceutical, Osaka, Japan) and allowed 9 weeks to recover. Since OVX and sham-operated rats had reached 17 weeks old at the beginning of the experiment, these rats were classified as an adult group.

Throughout the experiments, the rats were housed in an automatic kaolin and food intake monitoring system (FDM700SW; Melquest, Toyama, Japan). Briefly, this system consists of an acrylic home cage ($26 \times 20 \times 23$ cm^3), two containers ($7 \times 4 \times 10$ cm^3), and a controller equipped with two load cells (weight sensor). Commercially available standard chow (CE-2; CLEA Japan, Inc., Tokyo, Japan) and hand-made kaolin pellets were provided in their respective containers. Kaolin pellets were prepared according to our previous method (Yamamoto et al., 2014). Briefly, pharmaceutical-grade kaolin (hydrated aluminum silicate) was mixed with 3% w/w gum arabic in distilled water to form pellets similar in size to chow pellets and these pellets were then completely dried at room temperature. Both intakes were recorded daily to the nearest 0.01 g using a laptop PC. The rats were habituated in a room with a regular light/dark cycle (lights on 0600–1800 h) at a constant temperature (25 ± 1 °C) and humidity (50 ± 5%), adapted to the experimental environment for at least 7 days, and allowed free access to tap water and both pellets throughout the experimental period.

On the day of the experiment, the rats subcutaneously received teriparatide (0.2 and 0.4 mg/kg) at a volume of 1 mg/kg at 1800 h. RSA was used to prevent the adsorption of teriparatide onto the tube surface. Controls were treated with vehicle (0.1% RSA saline solution). There were four to six rats in each of the experimental groups. After the completion of all experiments, the rats were euthanized with an overdose of sodium pentobarbital (150 mg/kg, i.p.).

2.2. Effects of anti-emetic agents on teriparatide-induced pica and anorexia in rats

Granisetron (serotonin 5-HT_3 receptor antagonist; 0.1, 0.5, and 1 mg/kg, i.p.), prochlorperazine (dopamine D_2 receptor antagonist; 0.1, 0.5, and 1 mg/kg, i.p.), fosaprepitant (neurokinin NK_1 receptor antagonist; 0.5, 1, and 2 mg/kg, i.p.), or diphenhydramine (histamine H_1 receptor antagonist; 5, 10, and 20 mg/kg, i.p.) was administered simultaneously with the subcutaneous administration of teriparatide (0.4 mg/kg, s.c.) to OVX rats and their daily levels of kaolin and food consumption were measured. The doses selected in this study were determined from our previous experience and published data (Fakhfouri et al., 2010; Ghelardini et al., 2004; Takeda et al., 1995; Yamamoto et al., 2014). Control animals received saline (1 ml/kg body weight, i.p.) as a substitute for anti-emetic drugs. There were four rats in each of the experimental groups. After the completion of all experiments, the rats were euthanized with an overdose of sodium pentobarbital (150 mg/kg, i.p.).

2.3. Drugs

Gum arabic, kaolin, and RSA were obtained from Sigma-Aldrich Japan (Tokyo, Japan). Granisetron hydrochloride (Kytril®; Chugai Pharmaceutical, Tokyo, Japan), prochlorperazine mesilate (Novamin®; Shionogi, Osaka, Japan), fosaprepitant dimeglumine (Proemend®; Ono Pharmaceutical, Osaka, Japan), and diphenhydramine hydrochloride (Resmin®; Nissin Pharmaceutical, Yamagata, Japan) were dissolved in physiological saline. Teriparatide was from Asahi Kasei Pharma Corp. (Tokyo, Japan) and dissolved in 0.1% RSA saline solution. All drugs were prepared immediately before injection. Doses are expressed as the free base.

2.4. Statistical analysis

Data are expressed as mean values ± S.E.M. Differences in means were analyzed using one-way analysis of variance (ANOVA), followed by post hoc Dunnett's multiple comparison tests. A P value of less than 0.05 was considered significant.