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Pica in Rats Is Analogous to Emesis: An Animal Model in Emesis Research

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TAKEDA, N., S. HASEGAWA, M. MORITA AND T. MATSUNAGA. *Pica in rats is analogous to emesis: An animal model in emesis research.* PHARMACOL BIOCHEM BEHAV 45(4) 817–821, 1993.—Mitchell et al. (1976, 1977) suggested that pica, eating of nonnutritive substances such as kaolin, is an illness-response behavior in rats. In the present study, we first confirmed their suggestion and then examined the effects of antiemetics on emetic-induced pica in rats. Intraperitoneal injection of apomorphine induced dose-dependent kaolin consumption. Pretreatment with domperidone inhibited apomorphine-induced kaolin intake. Oral administration of copper sulfate and intraperitoneal injection of cisplatin also induced dose-dependent kaolin consumption. Pretreatment with ondansetron inhibited cisplatin-induced kaolin intake. These findings suggest that pica in rats was induced through 1) dopamine D_2 receptors in the chemoreceptor trigger zone, and 2) the stomach, partly via 5-HT_3 receptors in the visceral afferents in the stomach wall. The present findings support the conclusion that pica in rats is analogous to vomiting in other species and suggest that pica in rats is mediated by the same mechanisms as vomiting in humans. Accordingly, we extended the utility of the animal model to pharmacological research of emesis with pica as an analogue to emesis.

Pica Emesis Apomorphine Domperidone Copper sulfate Cisplatin Ondansetron Animal model Rat

NAUSEA and vomiting are associated with many kinds of disease. However, research on emesis and antiemetics has been limited, partly because the only animal models available have been dogs and cats, which vomit in response to emetic stimuli and provocative motion (8,13), but which are expensive and difficult to handle. Recently, ferrets have also been used for studies on chemotherapy-induced emesis (10). But, common laboratory animals, such as rats, guinea pigs, and mice, cannot be used, because they do not vomit.

Mitchell et al. reported that poison or motion induce pica, eating nonnutritive substances such as kaolin (china clay), in rats and suggested that pica is an illness-response behavior analogous to vomiting in other species (16,17). They developed a rat animal model and demonstrated its utility in assaying for both motion sickness and the emetic properties of drugs.

In the present study, we first confirmed their suggestion and then examined the effects of antiemetics on emetic-induced pica in rats. Our results validated the analogy of pica in rats to vomiting in humans, and extended the pharmacological utility of the animal model by demonstrating that antiemetics, known to block emetic-induced vomiting in humans, also block emetic-induced pica in rats.

METHOD

Animals

Male Wistar strain rats weighing about 150 g (Kari Co., Japan) were used. They were housed in individual standard home cages (35 × 45 × 25 cm) with freely available food, water, and kaolin in a room with a 12L : 12D cycle (light from 0800–2000).

Kaolin

Kaolin was prepared by the methods of Mitchell et al. (16,17) with slight modifications. Pharmaceutical-grade kaolin (china clay, hydrated aluminum silicate, Fisher, USA) was mixed with 1% gum arabic (Ishizu Pharmaceutical Co., Japan) in distilled water to form a thick paste, which was extruded through a syringe onto wire mesh trays and partially dried at room temperature. This mixture was then introduced into a column of the same shape as that for food, and again dried completely at room temperature. The kaolin, provided in containers, was placed in the cage for 3 days before the experiment to allow the animals to become adapted to its presence. The kaolin container was removed, weighed to the nearest 0.1 g, refilled, and replaced at 1800 each day. Split

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TABLE 1
EXPERIMENTAL GROUPS

Apomorphine		Apomorphine (10 mg/kg) + Domperidone		Copper Sulfate		Cisplatin		Cisplatin (10 mg/kg) + Ondansetron	
Dose	*n*	Dose	*n*	Dose	*n*	Dose	*n*	Dose	*n*
1 mg/kg	13	saline + 0.01%		4 mg/kg	11	5 mg/kg	8	saline	8
5 mg/kg	13	Tween 20	5	8 mg/kg	11	10 mg/kg	8	1 mg/kg	6
10 mg/kg	13	1 mg/kg	5	20 mg/kg	11			2 mg/kg	8
		2 mg/kg	5	40 mg/kg	11				

n: number of animals.

kaolin was collected, dried, and weighed to obtain correct values for kaolin consumption.

Food

The rats were allowed free access to standard laboratory rat chow (Oriental Yeast, Japan). The food consumption was measured at 1800 each day.

Drug Administration

On the day of the experiment, test rats received drugs at 1800. Apomorphine (Sigma, USA) was dissolved in saline and injected intraperitoneally (IP). Domperidone (Kyowa Hakko, Co., Japan) was sonicated in saline containing 0.01% Tween 20 (Wako, Japan) and injected (IP) 10 min before the administration of apomorphine. Copper sulfate (Wako, Japan) was dissolved in saline and administered intragastrically (IG) through a blunt oral needle. Cisplatin (0.5 mg/ml, Bristol-Myers Squibb Co. Ltd., Japan) was injected (IP). Ondansetron (Nippon Glaxo Co., Japan) was dissolved in saline and injected (IP) 10 min before the administration of cisplatin. Kaolin intake for 24 h after drug administration was measured. The numbers of animals in each treatment condition are shown in Table 1.

Food intake for 24 h after administration of the drugs tested was measured in different rats. Test rats received domperidone (IP), ondansetron (IP), apomorphine (IP), cisplatin (IP), or copper sulfate (IG). Control rats received vehicle only. The numbers of animals in each treatment condition are shown in Table 2.

The statistical significance of differences was evaluated by Student's *t*-test.

TABLE 2
EFFECTS OF DOMPERIDONE, ONDANSETRON, APOMORPHINE, CISPLATIN, AND COPPER SULFATE ON FOOD CONSUMPTION IN RATS

	n	(g/day)
Saline + 0.01% Tween 20 (IP)	8	20.7 ± 0.8
Domperidone (2 mg/kg, IP)	8	21.4 ± 0.8
Saline (IP)	8	21.1 ± 0.6
Ondansetron (2 mg/kg, IP)	8	21.0 ± 0.7
Saline (IP)	8	21.9 ± 0.8
Apomorphine (10 mg/kg, IP)	8	20.1 ± 0.9
Cisplatin (10 mg/kg, IP)	8	10.8 ± 0.9*
Saline (IG)	8	18.4 ± 0.5
Copper sulfate (40 mg/kg, IG)	8	15.1 ± 1.0†

Values are means ± SE. *n*: number of animals.
*$p < 0.01$ vs. saline controls.
†$p < 0.05$ vs. saline controls.

RESULTS

Some rats ate a little kaolin on the 1st day of adaptation to the presence of kaolin, but they did not eat any kaolin during the next 2 days before the experiment.

Intraperitoneal injection of apomorphine at doses of 1, 5, and 10 mg/kg induced dose-dependent kaolin intake (Fig. 1). Intraperitoneal injection of domperidone at a dose of 1 or 2 mg/kg, 10 min before apomorphine (10 mg/kg, IP) administration, significantly inhibited this kaolin intake (Fig. 2). Per-oral administration of copper sulfate at doses of 4, 8, 20, and 40 mg/kg also induced dose-dependent kaolin consumption (Fig. 3). Intraperitoneal injection of cisplatin at doses of 5 and 10 mg/kg also induced kaolin intake in rats (Fig. 4). Intraperitoneal injection of ondansetron at a dose of 1 or 2 mg/kg, 10 min before cisplatin (10 mg/kg, IP) administration, significantly inhibited cisplatin-induced kaolin intake (Fig. 5). Intraperitoneal and oral administrations of saline and intraperitoneal injection of saline containing 0.01% Tween 20 did not induced kaolin intake in rats.

Domperidone (2 mg/kg, IP), ondansetron (2 mg/kg, IP), and apomorphine (10 mg/kg, IP) did not affect food intake of rats. However, food intake after injection of cisplatin (10 mg/kg, IP) significantly decreased. Copper sulfate at a dose

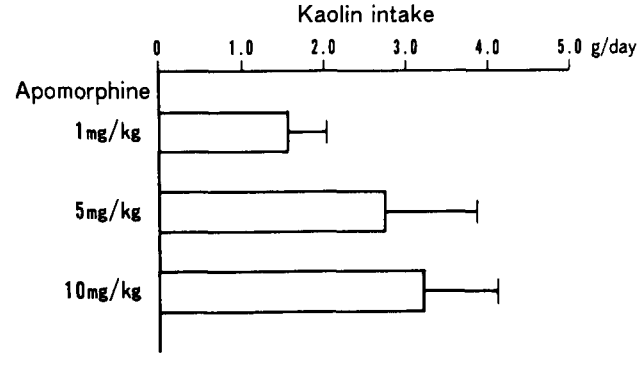

FIG. 1. Kaolin intake of rats induced by intraperitoneal injection of apomorphine. Columns and bars represent mean intake ± SE of 13 animals for 24 h after the injection.

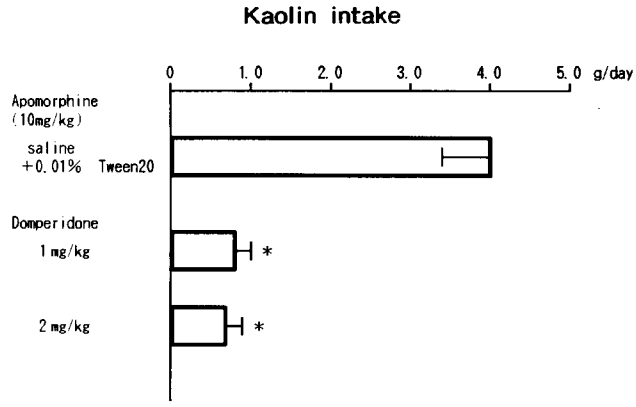

FIG. 2. Effect of intraperitoneal injection of domperidone on kaolin intake of rats induced by apomorphine (10 mg/kg, IP). Columns and bars represent mean values ± SE of kaolin intake of five animals for 24 h after injection of apomorphine. $*p < 0.01$ vs. vehicle control.

of 40 mg/kg (IG) slightly, but significantly, decreased food consumption (Table 2).

DISCUSSION

Intraperitoneal injection of apomorphine (1–10 mg/kg) induced dose-dependent kaolin consumption (Fig. 1). The chemoreceptor trigger zone (CTZ) is located in the area postrema in the floor of the fourth ventricle and is activated by chemical stimuli in the blood or cerebrospinal fluid. When stimulated, the CTZ activates the emetic center, resulting in emesis (5,26). Apomorphine is one of the emetics that act on the CTZ and induce vomiting in humans, dogs, cats, and ferrets (13,26). Therefore, our finding suggests an action at the CTZ in rats related to pica. Apomorphine is an agonist of the dopamine D_2 receptor, and domperidone, an antagonist of the D_2 receptor, inhibits vomiting induced by apomorphine in humans and dogs (6,27). In rats, domperidone (1–2 mg/kg, IP) also suppressed apomorphine (10 mg/kg, IP)-induced pica, suggesting that dopaminergic involvement in the CTZ of rats related to pica as in the CTZ of other species related to vomiting (Fig. 2).

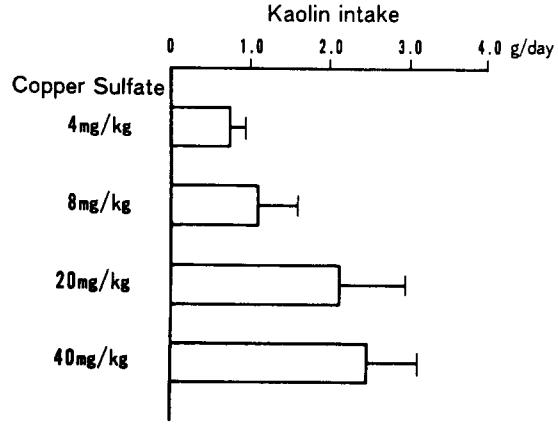

FIG. 3. Kaolin intake of rats induced by peroral administration of copper sulfate. Columns and bars represent mean intakes ± SE of 11 animals for 24 h after treatment.

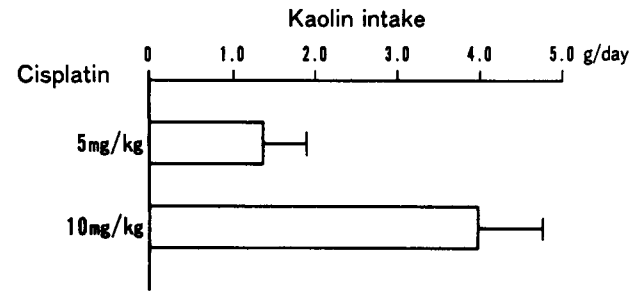

FIG. 4. Kaolin intake of rats induced by intraperitoneal injection of cisplatin. Columns and bars represent mean intakes ± SE of eight animals for 24 h after the injection.

Oral administration of copper sulfate (4–40 mg/kg) and intraperitoneal injection of cisplatin (5–10 mg/kg) also induced dose-dependent kaolin consumption (Figs. 3, 4). Intragastric copper sulfate stimulates the terminals of the visceral afferents innervating the stomach wall and causes vomiting in humans, dogs, cats, and ferrets (13,26). Therefore, afferent signals from the stomach also seem to induce pica in rats. Recently, studies demonstrated that cisplatin causes release of serotonin from enterochromaffin cells in the upper gastrointestinal tract and that this released serotonin stimulates the gastrointestinal visceral afferents via 5-HT_3 receptors, resulting in vomiting (1). Ondansetron, a selective 5-HT_3 antagonist, prevented cisplatin-induced vomiting in humans, dogs, and ferrets (2,23). In rats, ondansetron (1–2 mg/kg, IP) suppressed cisplatin-induced pica, suggesting that this serotoninergic pathway in the gastrointestinal tract is also involved in pica in rats (Fig. 5).

We have reported that pica was induced by double rotation with continuously changing centrifugal and angular accelerations. However, double rotation failed to induce pica in bilaterally labyrinthectomized rats (19). Since normal inner ear function is necessary for the development of motion sickness in humans (18,22), these findings suggest that rats also suffer from motion sickness due to sensory information passed through the inner ear. Furthermore, we have reported that motion sickness in rats was prevented by anti-motion sickness drugs that are effective in humans (20). Double rotation-induced pica was inhibited by intraperitoneal injection of di-

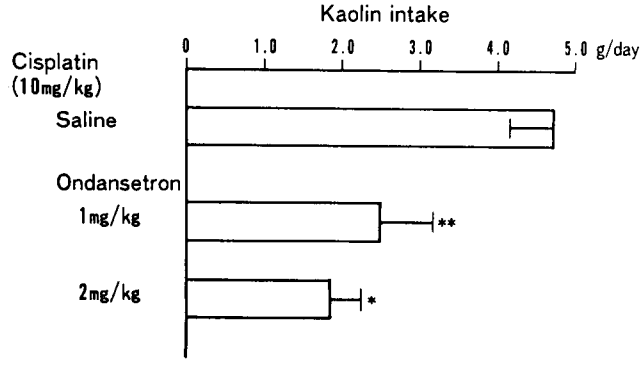

FIG. 5. Effect of intraperitoneal injection of ondansetron on kaolin intake of rats induced by cisplatin (10 mg/kg, IP). Columns and bars represent mean values ± SE of kaolin intake for 24 h after injection of cisplatin at 1 mg/kg (six animals) or 2 mg/kg (eight animals) or saline (eight animals). $**p < 0.05$, $*p < 0.01$ vs. control.

phenhydramine, a histamine H_1 antagonist, and methanphetamine, a catecholamine releaser. Transdermal administration of scopolamine, an acetylcholine muscarinic antagonist, also reduced the rotation-induced kaolin intake in rats. Therefore, the same histaminergic, catecholaminergic, and cholinergic mechanisms as in humans are apparently involved in motion sickness in rats (24).

Mitchell et al. reported that a variety of orally and injection-administered toxins and emetics (lithium chloride, Red Squill, cyclophosphamide) elicited dose-dependent pica in rats (16). The present findings that apomorphine, copper sulfate, and cisplatin induced dose-dependent kaolin intake confirmed their previous report of dose dependence. They also reported that motion sickness caused rats to engaged in pica and that motion-induced pica showed the same set of characteristics (variability, summation, habituation, and recovery) as shown by other species in which emesis is used to assay for motion sickness (17). Our previous finding that double rotation induced kaolin intake supported their previous report of motion sickness. Thus, our present and previous findings are consistent with their conclusion that pica in rats is analogous to vomiting in other species. Moreover, our findings demonstrated that pica in rats is mediated by the same mechanisms and through the same receptors as vomiting in humans and other species that vomit. Accordingly, in the present study we extended the utility of the animal model to pharmacological research of emesis.

Domperidone (2 mg/kg, IP) and ondansetron (2 mg/kg, IP) did not suppress food intake. This finding excludes the possibility that the antiemectic drugs tested inhibit feeding, but not pica.

In animals that vomit, emetic information from the CTZ, abdominal viscera, and vestibular system converge on the vomiting center in the brain stem, which acts in concert to coordinate the various processes involved in expelling the gastric contents (3,4). The vomiting center is represented by neural interactions between the nucleus tractus solitarius, the paraventricular reticular formation, and the visceral and somatomotor nuclei in the brain stem (15). Although rats do not vomit, they have the same brain stem nuclei. The present study demonstrates that they respond to three independent emetic stimuli that cause vomiting in other species. Therefore, rats probably lack the complex synaptic interactions among the brain stem nuclei necessary for the motor component of vomiting. According to the hierarchically organized defence mechanisms for protection of the body against toxins (9), the first-level defence mechanisms, such as smell and taste, are highly developed in rats. Rats identify toxic food by smell and taste without swallowing it, reject it, and form an aversion to it (11,12). Rats also have a second-level defence system of gastric chemoreceptors (7). They do not induce vomiting, but pica is probably a second-level defence mechanism, because kaolin or soil are good adsorbents and would adsorb a toxin ingested by chance, preventing it from being absorbed from the gastrointestinal tract.

Dogs, cats, and recently ferrets have been used for emesis research, but they are large and rather expensive. Monkeys may be a primate model, but they do not respond to apomorphine, a typical emetic in humans (13). *Suncus murinus* is the smallest mammal that vomits in response to a variety of emetics and provocative motion. But, this animal has no emetic CTZ (25). In the present study, we demonstrated that pica in rats is induced by the same pharmacological stimuli as vomiting in humans and that antiemetics, known to block emetic-induced vomiting in humans, block emetic-induced pica in rats. The findings support the conclusion that pica in rats is analogous to vomiting in other species (16,17) and suggest that pica in rats is mediated by the same mechanisms as vomiting in humans. We extended the utility of the animal model to pharmacological research of emesis with pica as an analogue to emesis, especially the development of new antiemetics.

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