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Pica as an adaptive response: Kaolin consumption helps rats recover from chemotherapy-induced illness

Bart C. De Jonghe, Maureen P. Lawler, Charles C. Horn^{*}, and Michael G. Tordoff

Monell Chemical Senses Center, Philadelphia, PA 19104, USA

Abstract

Clay consumption can occur during illness but there has been little work to understand why. To investigate whether consuming clay confers an advantage to the sick animal, we compared the recovery from illness of adult male rats with or without access to kaolin. Illness was induced by injection of 6 mg/kg, ip, cisplatin, a toxic chemotherapy agent, and recovery was assessed by changes in daily food intake, water intake, and body weight. Relative to saline-injected controls, cisplatin-injected rats reduced food and water intake and lost weight. However, those with access to kaolin ate more food and lost less body weight than did those without access to kaolin. Thus, clay consumption appeared beneficial in that it either protected the rats from illness or enhanced recovery and might prove useful as an adjunct therapy for other animals, including humans, experiencing visceral malaise.

Keywords

Nausea; Emesis; Pica; clay; Cisplatin; vagus

1. Introduction

Geophagia, a form of pica (ingestion of non-nutritive substances), is common in many species and has been prevalent throughout human history [1–3]. Although also commonly associated with aberrant behavior leading to toxicity-related disease, e.g., lead poisoning [4], medicinal treatment properties of geophagia have been reported in historical literature for more than 1000 years [2,5]. Several explanations for geophagia have been offered. Under some circumstances, ingestion may provide scarce micronutrients such as iron or calcium [6,7]. Clay may also alter gastrointestinal transit and absorption, or serve to bind or dilute a toxin in the gastrointestinal tract, thus reducing its adverse effects [8–10]. In human societies, culture may also determine whether and when clay is consumed [11,12].

Geophagia is not always adaptive. Hooper and Mann postulated that pica can be at first advantageous, but continued ingestion of clay or earth may lead to prolonged malabsorption of essential nutrients, that render pica as self-propagating and unnecessarily harmful (see [13] for discussion). For example, rats fed a maintenance diet mixed with kaolin, before and during pregnancy, had decreased hematocrit and hemoglobin levels as well as diminished red blood

^{*}Address correspondence to: Charles C. Horn, PhD, Monell Chemical Senses Center, 3500 Market St, Philadelphia, PA 19104, Telephone: 267-519-4865, Fax: 215-898-2084, Email: E-mail: horn@monell.org.

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cell counts and low birth weight in pups [14]. However, this paradigm may not be relevant because rats were forced to consume kaolin to get energy, which is unlike the method used here, where rats could choose kaolin alone, independent of an energy source.

The anti-neoplastic agent cisplatin, a common chemotherapy agent, exerts its cytotoxic effects primarily through direct interference with DNA synthesis, replication, or repair [see [15] for review]. Cisplatin has many deleterious side effects including the stimulation of nausea, vomiting, anorexia and behaviors indicative of malaise [16,17]. The source of emesis induced by cisplatin appears to stem from the release of serotonin from enterochromaffin cells that activates vagal afferent fibers containing 5-HT₃ receptors [see [18] for review], yet the specific neurobiological systems responsible for how this drug generates nausea and anorexia are for the most part undefined.

Intake of kaolin clay has been used as a marker for illness from a wide variety of stimuli, including cisplatin [19–22]. In the rat, kaolin intake has been used as a proxy for emesis [20] since this species does not vomit. Similar to the action of cisplatin on emesis, cisplatin-induced kaolin consumption in the rat is largely dependent on an intact gastrointestinal vagus [22] and is inhibited by common anti-emetic drugs, such as 5-HT₃ and NK₁ receptor antagonists, as well as corticosteroids [20,23,24]. However, it is unknown whether the appearance of pica induced by malaise is merely an indicator of illness, or if the behavior also has an ameliorative effect to improve the welfare of the animal. Therefore, in the current study we examined whether access to kaolin influenced recovery from cisplatin-induced illness, using changes in body weight, food intake and water intake as indicators of sickness. If kaolin access is effective for reducing illness, as indicated by these measures, it implies that kaolin consumption might have therapeutic benefits.

In a previous report, access to kaolin did not influence daily food intake or body weight gain of rats that were treated weekly with a low (1 mg/kg) dose of cisplatin [21]. This caused small and transient reductions in food intake such that recovery to baseline levels occurred within 1 or 2 days, and so was not conducive for observing kaolin-related influences on recovery. Our study used a single dose of cisplatin (6 mg/kg) that consistently produces prolonged reductions in body weight and food intake [19,22].

2. Methods

2.1. Subjects and experimental design

Sixty-seven male Sprague Dawley rats (Charles River; Kingston, NY) were housed individually in mesh-floored stainless-steel hanging cages (25 × 18 × 19 cm) and maintained in a temperature-controlled vivarium (~23°C), with a 12:12-h light-dark cycle (lights on at 0600). Animals were handled daily for two weeks prior to the onset of experiments. All rats had access to deionized water and powdered rat chow (PMI Nutrition, LabDiet 5001). Thirty-eight of the sixty-seven rats also had pelleted kaolin clay (aluminum silicate; Research Diets, Inc), which was available from a stainless steel hopper mounted to the back of the cage.

The experiment consisted of a 7-day baseline period followed by a 14-day recovery period. Throughout the experiment, body weight, and intakes of kaolin, food and water were measured every 24 h at ~1000 h. To accurately account for all intake, spillage of chow and kaolin was also weighed (all measurements to the nearest 0.1 g). Occasionally, spillage was too severe to allow a reasonable estimate of intake to be made (i.e., 4 kaolin, 1 food and 18 water measurements were lost out of 3,612 values due to kaolin mixed extensively with water and feces, a food cup turned over, or water bottles that were dropped or had loose stoppers). In these cases, the mean group value for a given day was substituted for an individual value.

After seven days of baseline measurements, rats were assigned to four groups matched for body weights and, if available, average daily kaolin intakes. Prior to injection, rats in the four groups had similar body weights: kaolin-saline (389 ± 4 g, $n = 19$), kaolin-cisplatin (392 ± 6 g, $n = 19$), no kaolin-saline (390 ± 5 g, $n = 15$), and no kaolin-cisplatin (389 ± 5 g, $n = 14$). The rats were injected (ip) with 0.9% saline (1 ml/kg body weight) or cisplatin (6 mg/ml/kg body weight; Sigma; MW = 300.1). Each rat received only one injection. More rats were assigned to the groups with access to kaolin because previous work led us to suspect their responses would be slightly more variable in consumption of food, kaolin, or water and maintenance of body weight. Cisplatin was prepared in 0.9% saline. The dose of cisplatin was chosen based on previous studies showing reliable induction of pica and suppression of feeding [20,22]. The protocol was approved by the Monell Chemical Senses Center Institutional Animal Care and Use Committee.

2.2. Statistical Analysis

Body weight, food, water, and kaolin intake data are expressed as means $\pm$ SEM. Each of the four measures was analyzed independently. A two-way mixed design ANOVA was used to analyze kaolin intake with Injection (saline or cisplatin) and Day (15 days; 1 day before and 14 days after injection) as factors. Planned comparisons of means were conducted on kaolin intake data using the Benjamini-Hochberg correction for multiple pair-wise tests [25]. This correction results in an alpha level of 0.025 or less. Three-way ANOVAs were performed on measures of body weight, food intake, and water intake with Injection (saline or cisplatin), Kaolin (kaolin access or no kaolin access), and Day (15 days) as factors. When three-way ANOVAs were statistically significant, two-way ANOVAs on specific days were conducted to determine the interaction effects of Injection (saline or cisplatin) and Kaolin (kaolin access or no kaolin access). The results of ANOVA were considered statistically significant if $p < 0.05$. To further explore the relationship between kaolin intake, food intake, and body weight these measures were compared using Pearson correlation coefficients in cisplatin-treated animals. Up to 5 days, baseline, prior to injection were included in the correlation analysis. Statistical analyses were computed using Statistica (Version 8; Statsoft) and SigmaStat (Version 3.5; Systat).

3. Results

3.1. Cisplatin-induced pica

Cisplatin treatment significantly increased kaolin intake in rats with kaolin access [Injection $\times$ Day interaction; $F(14, 504) = 3.7$, $p < 0.00001$]. On Days 1, 2, 4, 5 and 11 after cisplatin injection kaolin intake was significantly higher than the comparable group given saline (Fig. 1A; Benjamini-Hochberg corrected mean comparisons).

3.2. Cisplatin-induced reduction in body weight

Cisplatin caused all rats to lose body weight but less in rats with access to kaolin than without it [Injection $\times$ Kaolin access $\times$ Day interaction; $F(14, 882) = 2.6$, $p < 0.005$]. There were no statistically significant two-way interactions (Injection $\times$ Kaolin access) for any specific Day (Fig. 1B).

3.3. Cisplatin-induced reduction in food intake

Cisplatin reduced food intake but less so in rats with access to kaolin than those without it [Injection $\times$ Kaolin access $\times$ Day interaction; $F(14, 882) = 3.0$, $p < 0.0005$]. Kaolin access played a significant role to reduce anorexia produced by cisplatin injection on Days 3, 4, 5, and 11 after injection [Injection $\times$ Kaolin access interactions; F 's(1,63) ≥ 4.2 , p 's < 0.05 , Fig. 1C].

3.4. Cisplatin-induced changes in water consumption

Cisplatin induced significant changes in water intake over the post-injection Days [Injection $\times$ Day interaction, $F(14,882) = 16.8$, $p < 0.000001$], but there was no difference between the groups with or without kaolin [the 3-way interaction was not significant, $p = 0.4$].

3.5. Correlations between food, water, and kaolin intake and body weight

In animals injected with cisplatin, there was a strong positive relationship between food intake and body weight before and after cisplatin treatment (r 's = 0.5 to 0.9, p 's < 0.05). Only on Day 2 post-injection in animals without kaolin access was the relationship between food intake and body weight not statistically significant ($r = 0.46$, $p > 0.05$). Before or after injection with cisplatin, water intake and body weight were positively correlated in groups with and without kaolin (kaolin group, Days -5, -3, 1, 2, 3, and 4, r 's ≥ 0.5 , and no kaolin group, Days -4, -1, 4, 10, and 14, r 's ≥ 0.6 , p 's < 0.05). In cisplatin treated animals with access to kaolin, there were few significant correlations between kaolin intake and other measures: with water intake on Day 14 ($r = 0.6$, $p < 0.05$) and a negative correlation with food intake on Days -4, 9, 10, and 11 (r 's ≥ -0.5 , p 's < 0.05).

4. Discussion

Cisplatin caused hypophagia and weight loss in all rats but these symptoms of illness were less severe in rats with access to kaolin than in those without. These data suggest that kaolin consumption following cisplatin not only indicates sickness but also plays a therapeutic role by diminishing the degree of malaise experienced by the rat and/or enhancing the rate of recovery.

The mechanism by which kaolin consumption affects the recovery from cisplatin-induced malaise is unknown. After systemic treatment with cisplatin in rats, platinum is primarily excreted in the urine with a rapid elimination within the first day of treatment and a less rapid loss for at least 30 days [26]. Cisplatin produces gastric stasis and diarrhea [19,27,28] and there are reports of small amounts of platinum present in the intestine and feces after systemic injection of cisplatin in mice and dogs [29,30]. Clay possesses toxin-binding properties [8,9] and kaolin is an anti-diarrhea agent [31]; therefore, these actions might limit the adverse effects of cisplatin on the GI tract, lessening the severity of distress experienced by the animal.

Kaolin intake was associated with improved food intake in rats treated with cisplatin but the temporal relationship was not straightforward. Kaolin intake was highest on day 1 after cisplatin treatment but food intake was not significantly affected by kaolin access until day 3. This indicates the possibility of a more complex relationship between kaolin intake and food consumption in rats recovering from cisplatin treatment. For example, high kaolin intake on day 1 after cisplatin injection might lead to improved food intake over the next several days despite the fact that kaolin intake is lower on these days. There were few statistically significant correlations between measures for food intake, water intake, and body weight that might differentiate animals with or without access to kaolin and treated with cisplatin (see Results).

Our results show that kaolin consumption ameliorates cisplatin-induced reductions in food but not water intake. This might be explained by the different mechanisms that underlie food and water transit and absorption in the gut. Nephrotoxicity is a common side effect of cisplatin treatment [32,33] and increased water intake has been noted in several studies [19,22]. It seems unlikely that kaolin intake could lessen the impact of nephrotoxicity produced by cisplatin and this might explain why kaolin ingestion does not reduce the effect of cisplatin on water intake.

The physiology of pica and the biological basis for the drive to consume clay are still a mystery. However, it is important to determine the mechanisms involved because apart from conditioned

flavor aversion testing, pica is the primary metric to assess malaise in the non-vomiting rat. It will be important in future experiments to determine the effect of kaolin access on conditioned flavor aversion. Chemotherapy treatments produce conditioned flavor aversions in rats and is a common problem in cancer patients [34–36]. Attempts to block pica in rodents by pharmacological means, for example, in a search for drug candidates to control emesis, might actually lead to a poorer health outcomes since a potential therapeutic strategy is inhibited. Overall, the current data show that kaolin access improves the health of the rat following cisplatin treatment, supporting reports of beneficial effects of clay consumption. It is possible that clay intake could provide an inexpensive therapeutic adjunct for patients receiving chemotherapy.

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Fig. 1.

Effects of cisplatin, a chemotherapy agent, on kaolin consumption and body weight, food intake, and water intake in rats with or without kaolin access. One day of baseline measures is shown (Day 0) before injection (ip) of Cisplatin (6 mg/kg) or saline. The dashed vertical line indicates the time of injection. **A)** Cisplatin increased kaolin consumption in rats with access to kaolin. * = statistically significant mean comparison for saline vs. cisplatin, Benjamini-Hochberg correction for multiple comparisons. **B)** Effects of cisplatin on body weight, **C)** food intake, and **D)** water consumption in animals with or without kaolin access. “ α ” = $p < 0.05$, significant two-way ANOVAs, injection by kaolin access for food intake at 3, 4, 5, and 11 days after injection.