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Running induces nausea in rats: Kaolin intake generated by voluntary and forced wheel running

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ABSTRACT

Three experiments were conducted showing rats' pica behavior (kaolin clay intake) due to running in activity wheels. The amount of kaolin consumed was a positive function of the available time of voluntary running (20, 40, or 60 min), although this relationship was blunted by a descending (i.e., 60 → 40 → 20 min) test series of execution (Experiment 1). Pica was also generated by forced running in a motorized wheel for 60 min as a positive function of the speed of wheel rotations at 98, 185, or 365 m/h, independent of the order of execution (Experiment 2). Voluntary running generated more pica than did forced running at 80 m/h, although the distance travelled in the former condition was 27% lesser than that in the latter condition (Experiment 3). Because kaolin intake is regarded as a reliable measure of nausea in rats, these results show that wheel running, either voluntary or forced, induces nausea in rats.

1. Introduction

Rats engage in aberrant pica behavior (kaolin clay ingestion) after various nausea-inducing treatments, including irradiation (Yamamoto, Asano, Matsukawa, Imaizumi, & Yamatodani, 2011; Yamamoto, Takeda, & Yamatodani, 2002), motion sickness (McCaffrey, 1985; Mitchell, Krusemark, & Hafner, 1977; Mitchell, Laycock, & Stephens, 1977; Morita, Takeda, Kubo, & Matsunaga, 1988; Morita, Takeda, Kubo, Yamatodani, et al., 1988; Takeda et al., 1995a), and administration of emetogenic drugs such as lithium chloride (LiCl: Mitchell et al., 1976; Watson & Leitner, 1988; Yamamoto, Ngan, Takeda, Yamatodani, & Rudd, 2004), cyclophosphamide (Mitchell et al., 1976; Tohei, Kojima, Ikeda, Hokao, & Shinoda, 2011; Yamamoto, Nakai, Nohara, & Yamatodani, 2007; Yamamoto et al., 2011), cisplatin (De Jonghe & Horn, 2008; De Jonghe, Lawler, Horn, & Tordoff, 2009; Han et al., 2014; Horn, De Jonghe, Matyas, & Norgren, 2009; Liu, Malik, Sanger, Friedman, & Andrews, 2005; Malik, Liu, Cole, Sanger, & Andrews, 2007; Rudd, Yamamoto, Yamatodani, & Takeda, 2002; Saeki et al., 2001; Sharma, Gupta, Kochupillai, Seth, & Gupta, 1997; Takeda et al., 1995b; Takeda, Hasegawa, Morita, & Matsunaga, 1993; Yamamoto et al., 2007, 2011, 2014), morphine (Aung, Mehendale, Xie, Moss, & Yuan, 2004), apomorphine (De Jonghe & Horn, 2008; Takeda et al., 1995a, 1993), nicotine (Yamamoto et al., 2004), copper sulfate (Takeda et al., 1993; Yamamoto et al., 2004), ritonavir (Aung et al., 2005; Yuan et al., 2009), 2-deoxy-D-glucose (Watson & Leitner, 1988; Watson et al., 1987), cholecystokinin octapeptide (McCutcheon, Ballard, & McCaffrey, 1992), actinomycin D (Yamamoto et al., 2007), 5-fluorouracil (Yamamoto et al., 2007), and intragastric ethanol ingestion (Constancio, Pereira-Derderian, Menani, & De Luca, 2011). Pica generated by the above treatments can be attenuated by administering anti-emetic drugs (Takeda et al., 1995a, 1995b, 1993; Yamamoto et al., 2011, 2014, 2002; Aung et al., 2005, 2004; Han et al., 2014; Malik et al., 2007; Morita, Takeda, Kubo, Yamatodani, et al., 1988; Rudd et al., 2002; Saeki et al., 2001; Sharma et al., 1997; Tohei et al., 2011; Yuan et al., 2009). These studies strongly suggest that pica behavior is a good index of nausea (or gastrointestinal discomfort) in rats that cannot vomit because of anatomical and/or neural reasons (Horn et al., 2013).

Recent research from my laboratory (Nakajima & Katayama, 2014) demonstrated that pica behavior is also generated by voluntary running in a closed activity wheel, implying that running induces nausea in rats. Notably, other sources of information support this reasoning. First, running in an activity wheel establishes Pavlovian conditioned taste aversion (CTA) in rats to a tastant consumed shortly before running (e.g. Heth, Inglis, Russell, & Pierce, 2001; Lett & Grant, 1996; Lett, Grant, & Gaborko, 1998; Nakajima, Hayashi, & Kato, 2000; see Boakes & Nakajima, 2009; for a review), and this running-based CTA is prevented by administration of the anti-emetic granisetron (Eccles, Kim, & O'Hare,

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2005), supporting the hypothesis that nausea is the underlying physiological factor for establishing running-based CTA. Second, running-based CTA is alleviated not only by preexposure to running but also by prior injection of LiCl (Nakajima, Urata, & Ogawa, 2006), implying that a common process (presumably nausea) is physiologically habituated by preexposure. Third, a unique reduction in taste palatability, measured by the microstructure of rats' licking, accompanies running- and LiCl-based CTAs, indicating that running- and LiCl-based CTAs are commonly caused by nausea (Dwyer, Boakes, & Hayward, 2008).

Although these findings converge with the report of running-based pica behavior (Nakajima & Katayama, 2014), demonstration of increased kaolin consumption by voluntary running is novel, and calls for replication, which is provided in Experiment 1 of the present research. The major aim of Experiment 2 was to test the generality of finding, by using forced, rather than voluntary, running as an agent to evoke pica behavior. In these explorations, I manipulated the available time for voluntary running (Experiment 1) and the speed of forced running (Experiment 2) as critical independent variables. Finally, Experiment 3 directly compared the sizes of pica generated by voluntary and forced running treatments. In carrying out the research, Experiments 1 and 2 were conducted concurrently, while Experiment 3 was conducted after these experiments with half of the subjects of these experiments.

2. Experiment 1

In our previous research, a 60-min confinement in an unlocked wheel was employed for 4 successive days to demonstrate rats' pica behavior in their home cages (Nakajima & Katayama, 2014). It has been shown that the amount of pica positively depends on the dose of emetic treatments (Mitchell et al., 1976; Mitchell, Krusemark, et al., 1977; Yamamoto et al., 2002, 2004, 2007) and that the amount of running-based CTA is a positive function of length of available time for running (Hayashi, Nakajima, Urushihara, & Imada, 2002; Masaki & Nakajima, 2006). Therefore, I expected that the pica behavior would increase with the length of available time for running within a reasonable range. In this experiment, the available time was 20, 40, or 60 min, tested in an ascending or descending series of time length.

2.1. Method

2.1.1. Subjects and apparatus

Eight experimentally naïve male rats (Slc: Wistar/ST) were housed in individual wire home cages (20 cm wide, 25 cm long, and 18.7 cm high) in a vivarium on a 16:8-h light-dark cycle (lights on at 0800 h) at 23 °C and 55% humidity. The animals were 9 weeks old on the first day of this experiment, and they were maintained with food pellets, tap water, and kaolin pellets available ad libitum throughout the experiment.

The food pellets (MF diet; Oriental Yeast Co., Tokyo, Japan) were placed in a stainless container (7.5 cm wide, 4.5 cm long, 15 cm deep) positioned inwards with its end apertures 3.5 cm above the cage floor. The tap water was accessible from a stainless needle-pin nozzle protruding through a hole in the center of the back wall of each cage. The kaolin pellets were made of kaolin powder (Shin Nihon Zokei Co., Tokyo, Japan) and gum arabic (Holbein Works, Ltd., Osaka, Japan) at a 99:1 (w/w) ratio; they were mixed with tap water to form cylindrical pellets and were completely dried at room temperature. Each day, three or four kaolin pellets (about 20–25 g in total) were presented to each rat in a stainless steel bowl (8 cm in diameter and 3.5 cm deep) clipped to the cage wall at floor level with an iron hoop holder. A plastic tray (22.5 cm wide, 32 cm long, and 5.5 cm deep) with paper bedding was positioned 10 cm below each cage to collect excreta, food shatters, and kaolin splinters. Crushed kaolin and food in the tray were collected with a spoon and chopsticks, dried for a day, segregated, and weighed to obtain correct amounts of kaolin and food intake.

The rats were transferred, by a carrying cart having individual compartments, to a conventionally illuminated experimental room nearby, which had 8 hand-made activity wheels hung on a wire net arranged in a 4 × 2 fashion. The top and bottom rows were 140 and 90 cm above the room floor, respectively, and a long acrylic plate was fixed just below each row to catch excretions. Each wheel had an internal width of 15 cm and a diameter of 30 cm. The sides of the wheel were perforated metal sheets, and the running surface was made of 0.2-cm metal rods spaced 1 cm apart. The wheels could be tuned in both directions. The minimum torque to initiate the movement when the forepaws of animal were 10 cm from the lowest point of the unlocked wheel was around 25 cN measured by a Correx tension gauge (Haag-Streit A.G., Koeniz, Switzerland). A full turn of each wheel was counted automatically by a handcrafted system consisting of a small magnet on the outer rim of the wheel, a reed switch, and an electric pedometer fixed on the wire net. Each wheel could be locked by two plastic tied laundry pinches.

2.1.2. Procedure

At 1030 h of each day, all rats were weighed with an electric balance (KS-251, Dretec Co., Koshigaya, Japan) to the nearest 1 g and then moved to the individual compartments of the cart. On the initial 5 baseline days, the cart was kept in the vivarium for 60 min. On the next 4 days, animals were transferred to the experimental room, where half of the rats (Group 1) were allowed to run in the unlocked wheels for 60 min. For the other half of the rats (Group 2), the wheels were locked by the pinches 20 min after the onset of the running session and they were detained in the stationary wheels for the remaining 40 min. This procedure equated the durations in the experimental room between the two groups, but it inevitably resulted in the situation that the groups differed in the time elapsed between the end of running and returning to the home cages (i.e., the opportunity for kaolin consumption). Notably, this confounding factor seems unimportant, since in our observation the rats did not rush to consume kaolin after returning to the home cages.

After the second baseline treatment for 4 days, the running treatment was reinstated for 4 days with the available running time being 40 min for all rats; the animals were detained in the remaining 20 min in the locked wheels. After the third baseline treatment of 4 days, the final running phase was executed for 4 days: the length of available running time was 20 min (i.e., 40-min post-running detention) for Group 1 or 60 min for Group 2. Accordingly, the three running conditions (20, 40, and 60 min) were implemented in the descending series for Group 1, while they were in the ascending series for Group 2. The experiment ended with 2 baseline days.

2.1.3. Measurement

The amounts of food and kaolin consumed in the home cages (i.e., 23-h intakes) were recorded every day by removing the food and kaolin containers, immediately after the rats were moved to the individual compartments of the carrying cart. The containers were weighed with an electric balance (BJ-1500, Sartorius, K.K., Tokyo, Japan) to the nearest 0.1 g, refilled, and replaced at 1130 h, immediately before the rats were returned to the home cages. The experimental protocol was administered by laboratory assistants who were unaware of the purpose of the research.

2.1.4. Analysis

A paired-*t* test or an analysis of variance (ANOVA) was applied to each data set of interest. Pooled error term was used in subsequent