A GROUND-BASED ANIMAL MODEL OF SPACE ADAPTATION SYNDROME

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Abstract—We examined the effect and aftereffect of acute or chronic load of hypergravity produced by an animal centrifuge, on pica (that is, kaolin intake) in the rat as an index of motion sickness. Although the degree of pica initially induced by acute or chronic hypergravity was not different, the rate of decline of increased kaolin intake over poststimulus days was different. Pica after a 1-h load of 2g decreased rapidly. On the other hand, pica lasted 3 days after a 48-h load of 2g. These findings suggest that the aftereffects of chronic hypergravity application on pica are due to motion sickness induced by readaptation to normal gravity, and they support our idea that after adaptation to a hypergravity environment, return and readaptation to the normal gravity can simulate exposure and adaptation to microgravity. We concluded that motion sickness in rats induced by the aftereffects of chronic hypergravity stimulation can be used as a ground-based animal model of space adaptation syndrome. Copyright © 1996 Elsevier Science Inc.

Keywords—space adaptation syndrome; motion sickness; hypergravity; pica; rat.

Introduction

About 70% of the Shuttle astronauts experience space motion sickness during the initial 1 to 5 days of orbital flight (1). Symptoms range from malaise to vomiting, which reduces their performance and sense of well-being (2,3). Weightlessness alters the relationships among signals from the vestibular, visual, and proprioceptive receptors. Congruence between the converging inputs from the labyrinth, the eyes and the somatosensory receptors, and the expected sensory patterns that have been calibrated by prior experience of active locomotion is disrupted by the absence of gravity. This lack of congruence leads to neural mismatch, which appears to be the basic cause of space motion sickness (4,5). The adaptive processes whereby weightlessness rearranges the multisensory pattern of expectation in the brain occur as evidenced by the gradual and complete recovery from symptoms of space motion sickness (6). Space motion sickness can be viewed as a side effect of adaptation to weightlessness. This is why space motion sickness is officially called space adaptation syndrome by the National Aeronautics and Space Administration (NASA).

Mitchell and colleagues (7) suggested that pica is an illness-response behavior in rats, and we have demonstrated that pica in rats is analogous to vomiting in other species (8). We have also reported that pica was induced by rotation around two axes (double rotation) with continuously changing centrifugal and angular acceler-
ations. However, double rotation failed to induce pica in bilaterally labyrinthectomized rats (9). Since normal ear function is necessary for the development of motion sickness in humans, these findings suggest that rats also suffer from motion sickness due to vestibular information passed through the inner ear. Furthermore, we have demonstrated that double rotation-induced pica in rats was prevented by anti-motion-sickness drugs (diphenhydramine, scopolamine, and methamphetamine) that are effective in humans (10). These findings suggest that the pharmacological mechanisms for preventing motion sickness in rats and humans are similar. Therefore, we concluded that motion-induced pica can be used as an index of motion sickness in the rat.

In the present study, we attempted to develop a ground-based animal model of space adaptation syndrome on the basis of the following idea: in animals that had adapted to a chronic hypergravity environment, return and readaptation to the normal gravity can simulate exposure and adaptation to microgravity. For this purpose, we first developed an animal centrifuge device that produces hypergravity, and we used pica as an index of motion sickness in rats. We then examined the effects and aftereffects of acute or chronic load of hypergravity on pica in rats.

**Methods**

The animal experiments in this study were conducted under the guidelines approved by the Animal Care Committee of Osaka University Medical School.

**Animals**

Eighteen male Wistar rats weighing about 150 g were used. They were housed in individual home cages (35 × 45 × 25 cm) with free access to food, water, and kaolin in a room under a 12-hour light/dark cycle (light from 8:00 to 20:00). The animal room was maintained under standard laboratory conditions of temperature (22 ± 1°C) and relative humidity (55% ± 10%).

**Kaolin**

Kaolin (hydrated aluminum silicate, Fisher, USA) was mixed with 1% Arabic gum in 60% weight of hot distilled water. Consequently, the thick paste of the mixture was formed into a column of the same shape as the food pellets and was dried completely at room temperature. The kaolin, provided in a container, was placed in the home cage for 2 days before hypergravity testing to allow the animals to adapt to its presence. The consumption of kaolin in the container was determined by measuring its weight to the nearest 0.1 g at 17:00 every day. Spilt kaolin was collected, dried, and weighed to obtain correct values for kaolin consumption.

**Centrifuge Device**

Each animal was placed in an individual centrifuge cage (25 × 25 × 25 cm) and exposed to hypergravity on an animal centrifuge device (Figure 1). The swing arm on which the animal cage was suspended was mounted 50 cm from the axis of a turntable driven by a servo-controlled torque motor. The turntable was rotated at a constant rate, loading the animal in the centrifuge cage with the vector sum of the gravity linear acceleration vector and a rotation centrifugal linear acceleration vector. An angular velocity of 336°/s (56 rpm) achieved a resultant linear acceleration of 2g acting on the animal along the back-to-abdomen axis (2g centrifuge). The animal was free to move and was allowed free access to water, food, and kaolin in the centrifuge cage. Temperature was between 20 and 25°C, and relative humidity was between 60% and 70% before and during centrifugation. Kaolin consumption during centrifugation could not be measured because spilt kaolin could not be collected.

**Acute Hypergravity Experiment**

One group of 6 animals was used in this experiment. For the first 2 days prior to centrifugation, the animals were adapted to the experimental environment (they were placed in the
centrifuge cages for 1 h/day from 17:00 to 18:00, but were not rotated). Kaolin intake for 24 h after returning to the home cage was identified as that on pre-day 1 or 2. For the following 2 days, the animals were exposed to 2g centrifugation for 1 h/day from 17:00 to 18:00. Kaolin intake for 24 h after cessation of the second centrifugation was identified as that on post-day 1. The subsequent calendar days were identified as post-days 2 through 5.

Chronic Hypergravity Experiment 2

The other group of 5 animals was exposed to 2g centrifugation continuously for 24 h. All other experimental procedures were the same as those on chronic hypergravity experiment 1.

Statistical Analysis

In each acute and chronic hypergravity experiment, changes of kaolin intake were tested by one-way analysis of variance (ANOVA) with repeated measures. When appropriate, multiple comparison was made with the Student’s t test. Interaction between duration of hypergravity load and change of kaolin intake on
days after hypergravity load was tested by two-way repeated measures ANOVA.

Results

Rats ate only a small amount of kaolin on pre-days 1 and 2 (0.3 ± 0.1 g on pre-day 1, 0.3 ± 0.1 g on pre-day 2; mean ± SE, n = 18). In the acute hypergravity experiment, kaolin intake was significantly increased ($F[6, 30] = 14.1, P < 0.01$). Kaolin intake after the first centrifugation was less than that after the second one. Kaolin intake on post-day 1 (the initial 24-h period after the second 2g centrifugation for 1 h) was 5.2 ± 1.2 g (mean ± SE, n = 6), which was significantly higher than that on pre-days 1 and 2 ($P < 0.01$). Kaolin intake on post-day 2 (2.0 ± 0.7 g) was slightly, but not significantly, higher than that on pre-days 1 and 2, and was significantly less than that on post-day 1 ($P < 0.05$). Kaolin intake on post-days 3 through 5 was also significantly lower than that on post-day 1 ($P < 0.05$) (Figure 2).

In the chronic hypergravity experiment 1, kaolin intake was significantly increased ($F[6, 24] = 23.7, P < 0.01$). The animals ate 4.8 ± 0.7 g (mean ± SE, n = 5) of kaolin on post-day 1, which was significantly increased in comparison with that on pre-days 1 and 2 ($P < 0.01$). Kaolin intake on post-days 2 through 5 was gradually decreased. Kaolin intake on post-days 2 and 3, but not on post-days 4 and 5, was still significantly higher than that on pre-days 1 and 2 ($P < 0.05$). Kaolin intake on post-days 3, 4, and 5 was significantly lower than that on post-day 1 ($P < 0.01$) (Figure 3).

In the chronic hypergravity experiment 2, kaolin intake was significantly increased ($F[6, 24] = 23.7, P < 0.01$). The animals ate 4.8 ± 0.7 g (mean ± SE, n = 5) of kaolin on post-day 1, which was significantly increased in comparison with that on pre-days 1 and 2 ($P < 0.01$). Kaolin intake on post-days 2 through 5 was gradually decreased. Kaolin intake on post-days 2 and 3 was still significantly higher than that on pre-days 1 and 2 ($P < 0.05$). Kaolin intake on post-days 3 through 5 was significantly lower than that on post-day 1 ($P < 0.01$) (Figure 4).

The duration of hypergravity (1 h, 24 h, or 48 h) significantly affected changes in kaolin intake over poststimulus days after hypergravity load ($F[8, 60] = 2.2, P < 0.05$). But, kaolin intake on post-day 1 after acute hypergravity for 1 h was not significantly different from that after
Figure 3. Effects and aftereffects of chronic hypergravity on kaolin consumption. Animals were exposed to 2g centrifugation for 48 h, indicated by horizontal black bar. Columns and bars represent mean intakes ± SE (n = 7). *P < 0.01, **P < 0.05 compared with pre-days 1 and 2; #P < 0.01 compared with post-day 1.

Changes in linear acceleration play a key role in the development of motion sickness (11, 12). In the present study, acute hypergravity for 1 h induced a significant increase of kaolin intake in rats on post-day 1 (Figure 2), suggesting that they suffered from motion sickness due to changes in linear acceleration along the back-to-abdomen axis.

The kaolin intake increase after the first acute hypergravity was less than that after the second one (Figure 2). Mitchell and colleagues (13) reported similar initial suppression of rotation-induced kaolin intake over daily stimulation, and MaCaffrey (14) demonstrated that it is due to increased levels of nonspecific stress.

However, change in linear acceleration resulting from motion of spacecraft at launch does not cause space motion sickness. The symptoms develop in space after the acceleration change. The effects and aftereffects of chronic hypergravity were examined in the present study. After 2g centrifugation for 48 h, the animals showed a significant increase in kaolin intake on post-day 1. Thereafter, even though there was no stimulation, they continued to eat significantly increased amounts of kaolin. On post-day 3, the kaolin intake was still significantly higher than that on pre-days 1 and 2 (Figure 3). These findings indicate that the aftereffects of chronic hypergravity load induced motion sickness that lasted for more than 3 days.

There are two explanations for the aftereffects: 1) residual sickness induced by changes in linear acceleration and 2) sickness induced by readaptation to normal gravity after chronic application of hypergravity. Irrespective of whether hypergravity was acute or chronic, kaolin intake on post-day 1 was not significantly different. Therefore, in both acute and chronic hypergravity stimulation, the positive change in gravity (from 1g to 2g) induced motion sickness to the same extent. However, the rate of decline of increase kaolin intake seems to depend on the
duration of hypergravity exposure. After the second acute hypergravity for 1 h, kaolin intake on post-day 2 decreased rapidly (Figure 2). On the other hand, a prolonged decline of increased kaolin intake was found after chronic hypergravity for 48 h (Figure 3). A decline of kaolin intake after hypergravity for 24 h showed an intermediate rate (Figure 4). The rate of decline of increased kaolin intake after chronic hypergravity for 48 h was significantly different from that after acute hypergravity for 1 h. Since chronic hypergravity stimulation would rearrange the multisensory pattern of expectation in the brain (6), it is considered that the negative change (from 2g to 1g) in gravity induced motion sickness in animals that had adapted to hypergravity. Chronic hypergravity stimulation induced long-lasting pica with much the same extent of initial pica as that by acute hypergravity stimulation. These findings suggest that the aftereffects of chronic hypergravity are due not to residual sickness induced by changes in linear acceleration, but to sickness induced by readaptation to the normal 1-g environment.

To understand the mechanisms of space motion sickness and to develop countermeasures for preventing it, a ground-based animal model that simulates the effect of weightlessness on the vestibular system should be developed (5). In the present study, we showed a prolonged decline of increased kaolin intake as an index of motion sickness of rats after chronic hypergravity exposure. We suggest that it was induced in the process of readapting to the normal 1-g environment after adaptation to a 2-g environment. These results support our idea that, after becoming adapted to hypergravity, the return and readaptation to the 1-g environment could simulate exposure and adaptation to microgravity, thereby simulating the dynamic environments of weightlessness in ground-based investigations. Actually, three European astronauts, after a long centrifuge run, experienced motion sickness symptoms similar to the symptoms of the space adaptation syndrome as experienced during their space flight (15). Another group also reported that long duration human centrifugation induced motion sickness afterwards (16). Therefore, it is concluded that motion sickness induced in rats by the aftereffects of chronic hypergravity stimulation can be used as a ground-based animal model of space adaptation syndrome.

Figure 4. Effects and aftereffects of chronic hypergravity on kaolin consumption. Animals were exposed to 2g centrifugation for 24 h, indicated by horizontal black bar. Columns and bars represent mean intakes ± SE (n = 5). *P < 0.01, **P < 0.05 compared with pre-days 1 and 2, #P < 0.01 compared with post-day 1.
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