OPPOSITE EFFECTS OF MORPHINE ON FEEDING AND DRINKING IN RATS RELATIVE TO ADMINISTRATION TIME

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Abstract—The present study was undertaken to examine how morphine changes food and water intake in non-fasted or fasted rats with different administration times. Morphine (1, 3 and 10 mg/kg) was intraperitoneally administered at 10:45 (light period) or 18:45 (dark period). Morphine increased food and water intake in non-fasted rats 2 hr after the administration during the light period, whereas the total daily intakes were decreased. In contrast, morphine decreased food and water intake in non-fasted rats during the dark period and in fasted rats during both the light and dark period. These results suggest that morphine disorders the baseline levels of feeding and water drinking of naive rats.

Many investigations have shown that naloxone, a specific opiate antagonist, reduced food and water intake in non-fasted (1, 2) and fasted rats (3-5). Brown et al. (6) and Sanger et al. (7) indicated that these suppressions by naloxone are mediated through the blockade of endogenous opiate receptors (\(\mu\) receptors). If this contention is valid, morphine, an opiate agonist, might facilitate feeding and water drinking in non-fasted and fasted rats. Recently, many reports revealed the increments of food and water intake by morphine in non-fasted rats (8-11). Grandison and Guidotti also showed that intrahypothalamic administration of \(\beta\)-endorphin, an endogeneous opiate peptide, increased food and water intake in satiated rats (12). However, a few reports have shown that morphine suppresses such behaviors in fasted rats (13-15). These reports suggest the possibility that the effects of morphine on feeding and water drinking behavior are changeable under various circumstances.

The present study was undertaken to examine the effects of morphine under various conditions, and thus morphine was injected in non-fasted or fasted rats at different administration times (light or dark period).

Materials and Methods

Animals: Male Sprague-Dawley strain rats weighing 250-270 g were used. Each animal was housed individually in a hanging wire mesh cage (40 cm × 25 cm length × 20 cm height). The animal room was maintained at 23±1°C, with 55±5% relative humidity and on a 12 hr light-dark cycle (lights on 07:00 to 19:00). Powder chow (MF, Oriental Yeast Co., Tokyo) in a glass cylindrical vessel (8 cm diameter × 5 cm height) was used in the food intake study to minimize food spillage. A water tap with a Touch-n-Drink valve (Tokiwa Kagakukiki Co., Tokyo) was employed in the water drinking study to prevent water from spilling. The animals were given powder chow and water ad libitum, and they were trained on the powder chow and water tap at least for 7 days prior to the experiments.

In the study using fasted rats, the animals were deprived of food for 18-24 hr before the experiments.
**Experimental designs:** The administration of morphine was performed under the following 4 experimental conditions: 1) light period in non-fasted rats, 2) dark period in non-fasted rats, 3) light period in fasted rats, 4) dark period in fasted rats. One experiment was made up of 4 groups: saline (control)- and 3 morphine (1, 3 and 10 mg/kg)-treated groups. Each group consisted of 8 animals.

In the case of administration during the light period, saline or morphine was intraperitoneally injected at 10:45. Food vessels and water bottles were weighed at 2 hr intervals for 6 hr (at 11:00, 13:00, 15:00 and 17:00) and 24 hr after the food vessels and water bottles were supplied at 11:00. In the case of administration during the dark period, morphine was intraperitoneally injected at 18:45. The food vessels and water bottles were weighed at 19:00, 21:00, 23:00, 01:00 and 19:00 next day.

**Statistics:** The data obtained in this study were statistically analyzed by Student's *t*-test. The data were considered significant when the *P* value was less than 0.05 as compared to the saline control.

**Results**

**Effects of morphine during the light period in non-fasted rats:** The levels of food intake and water drinking in the control animal were very low throughout the 3 intervals (Fig. 1). Morphine significantly increased food intake in a dose-dependent manner in the 1st interval (11:00–13:00); however, all doses of morphine showed comparable levels to those of the control in the 2nd interval (13:00–15:00). In the 3rd interval (15:00–17:00), only the highest dose reduced food intake significantly. Morphine also changed water drinking similarly to food intake throughout the 3 intervals.

When total daily food intake and water drinking were determined, the higher two

![Fig. 1. Effects of morphine on food intake and water drinking during the light period in non-fasted rats. Morphine was administered i.p. at 10:45. Food intake and water drinking were measured for 6 hr at 2-hr intervals and for 24 hr after 11:00. Each group consisted of 8 animals. *P*<0.05 compared with the control.](image-url)
doses reduced these levels significantly.

Effects of morphine during the dark period in non-fasted rats: The levels of food intake and water drinking in the control animal were relatively high in the 1st interval (19:00–21:00) and gradually decreased during the last two intervals (21:00–23:00 and 23:00–01:00, Fig. 2). In the 1st and 2nd intervals, morphine markedly reduced food intake; especially, the highest dose showed significant changes. However, morphine caused no change in food intake in the 3rd interval, except for 3 mg/kg morphine which caused a significant increase. Morphine also showed similar changes in water drinking throughout the 3 intervals.

Morphine reduced total daily food intake and water drinking; however, only the highest dose showed significant changes.

Effects of morphine during the light period in fasted rats: The levels of food intake and water drinking in the control animals were very high at the 1st interval (11:00–13:00), but these levels were markedly reduced during the last two intervals (13:00–15:00 and 15:00–17:00, Fig. 3). In the 1st interval, morphine decreased food intake in a dose-dependent manner. In particular, the highest dose showed about 50% of the food intake of the control. The highest dose of morphine significantly increased food intake in the 2nd interval and decreased it in the 3rd interval. Morphine also showed similar changes in water drinking throughout the 3 intervals.

Morphine tended to decrease total daily food intake and water drinking. There were significant changes in 10 mg/kg-induced daily food intake and 3 mg/kg-induced daily water drinking.

Effects of morphine during the dark period in fasted rats: The levels of food intake and water drinking in the control animals were

Fig. 2. Effects of morphine on food intake and water drinking during the dark period in non-fasted rats. Morphine was administered i.p. at 18:45. Food intake and water drinking were measured for 6 hr at 2-hr intervals and for 24 hr after 19:00. Each group consisted of 8 animals. *P<0.05 compared with the control.
Fig. 3. Effects of morphine on food intake and water drinking during the light period in fasted rats. Morphine was administered i.p. at 10:45. Food intake and water drinking were measured for 6 hr at 2-hr intervals and for 24 hr after 11:00. Each group consisted of 8 animals. *P<0.05 compared with the control.

Fig. 4. Effects of morphine on food intake and water drinking during the dark period in fasted rats. Morphine was administered i.p. at 18:45. Food intake and water drinking were measured for 6 hr at 2-hr intervals and 24 hr after 19:00. Each group consisted of 8 animals. *P<0.05 compared with the control.
very high in the 1st interval (19:00–21:00) and were reduced during the last two intervals (21:00–23:00 and 23:00–01:00, Fig. 4). In the 1st interval, morphine decreased food intake in a dose-dependent manner; especially, the higher two doses showed significant changes. However, morphine showed the comparable levels of food intake to those of the control in the 2nd and 3rd intervals. Morphine changed water drinking almost similarly to food intake, but the highest dose significantly increased it in the 2nd interval, and the higher two doses significantly decreased it in the 3rd interval.

Morphine tended to reduce total daily food intake and water drinking; however, there were no significant changes except for the 10 mg/kg-induced daily food intake.

Discussion

The present study revealed that although 3 and 10 mg/kg of morphine suppressed ambulation for about 1 hr following the administration, morphine increased food and water drinking in non-fasted rats in the first 2 hr interval during the light period (Fig. 1). This result agrees with that of Sanger and McCarthy (16). They also reported that enkephalin and its analogues (RX7803 and ethylenkephalin) facilitated feeding and water drinking behavior in non-fasted rats during the light period (13). However, they showed that the levels of total daily food and water intake were not changed by morphine. In contrast, the present study indicated that morphine reduced the daily intakes in a dose-dependent manner (Fig. 1). Our data were obtained by measuring food intake and water drinking from 11:00 to 17:00. Although significant decrements were observed in the 3rd interval (15:00–17:00), the decreasing levels were too low to explain the decreasing levels of total daily food and water drinking. Therefore, it was suggested that morphine would suppress feeding and water drinking behavior during the dark period. Indeed, food intake and water drinking were reduced by morphine during the dark period in non-fasted rats (Fig. 2).

Decrement of food intake in fasted rats were made by morphine regardless of administration times (Figs. 3, 4). Even in non-fasted rats, feeding behavior was suppressed by morphine during the dark period (Fig. 2). Then, inhibition of ambulation in the 10 mg/kg of morphine-treated animals was observed only within the 10 min following the administration. The rats, being nocturnal animals, took about 80% of their daily food intake during the dark period in the present study. These results suggest that morphine disorders the baseline levels of the feeding behavior of naive rats. The present data also indicated that water drinking almost sympathized with food intake. This result is supported by the reports that drinking behavior depends on feeding behavior (17). We were therefore deeply interested in the present data showing that morphine had different effects on feeding and drinking behavior relative to the administration time and feeding condition. Recently, some investigations demonstrated that the suprachiasmatic nucleus (SCN), called an autonomous circadian pacemaker, exhibits high neural activities during the light period and low neural activities during the dark period in rats (18, 19). Oomura et al. reported that the SCN may inhibit feeding behavior because the SCN could stimulate the satiation centers in the ventromedial hypothalamic nucleus and inhibit the feeding centers in the lateral hypothalamic area (20, 21). They also explained that these changes and properties of the SCN neural activities would make the circadian rhythms of feeding and drinking behavior. From these reports, one possible estimation can be made for the effects of morphine, that is, morphine would inhibit the SCN neural activities to disorder the
feeding and water drinking behavior of naive rats.

There are many reports showing that food intake in fasted rats is reduced by naloxone. This suppressive effect of naloxone is shown not only in food deprivation, but also in hyperosmolarity, hypovolemia and angiotensin treatment (22). However, the present study revealed that morphine also decreased food intake and water drinking in fasted rats. Sanger and McCarthy (16) and Marks-Kaufman and Kanarek (23) reported the same results. Therefore, the disagreements between opiate agonist and antagonist are very strange but interesting. It is necessary to make more extensive efforts for elucidating the mechanisms of opiate agonists and antagonists on feeding and water drinking behavior.

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References


21) Oomura, Y. and Shibata, S.: Electrophysiological study of the relationship between suprachiasm-
