Effects of Oral Administration of Nicotine on Circadian Rhythms of Ambulatory Activity and Drinking in Rats
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Abstract—Effects of nicotine on circadian rhythms of ambulatory activity and drinking in male Wistar rats were examined. Nicotine was administered through the drinking water, and the daily doses of nicotine were adjusted to 0.5, 5 and 20 mg/kg/day. The treatment of nicotine induced a dose-dependent increase in ambulatory activity. On the other hand, fluid intake decreased at a dose of 20 mg/kg/day. Although the ambulatory activity and drinking were influenced by a long-term oral administration of nicotine, their circadian patterns, which were characteristic of nocturnal animals, were not altered.

The studies on nicotine chronically administered to animals are of pharmacological and toxicological importance. Although the chronic effects of nicotine on weight gain (1, 2), blood pressure (3, 4), and behaviors such as eating (5), drinking (1, 3, 5) and motor activity (6) in rodents have been extensively studied so far, there are few studies on the effects of nicotine on circadian rhythms of naive behaviors (7, 8). The present study was designed to examine the effects of nicotine on circadian patterns of ambulatory activity and drinking in rats.

Male Wistar rats (4 weeks of age) were individually housed in a wire mesh cage with free access to food and water under a light-dark cycle (light on from 6:00 to 18:00) with dawn and dusk periods (each over 2 hr) for 50 days. Measurements of ambulatory and drinking activities were carried out with an automatic apparatus (Model GT-831020: O’Hara and Co., Ltd., Tokyo). The principles of the device and the method for measurements of ambulatory activity and drinking in the rats were reported in detail by Tadokoro et al. (9). After the familiarization in a cage (ambulo-drinko cage) for 5 days, the ambulatory activity counts and those of the drinking (1 count=0.05 ml) were recorded every hour for 5 days. The periods of the measurements were from 6th to 10th day, from 16th to 20th day, from 26th to 30th day, from 36th to 40th day and from 46th to 50th day, respectively. Nicotine was administered to rats ad libitum by inclusion in the drinking water. The doses of nicotine were adjusted to 0.5, 5 and 20 mg/kg/day, respectively. The concentrations of the nicotine solutions were determined by two factors, the average of the consumed water and the average weight of the rats. The concentrations of the nicotine solutions for 50 days were 3.0–5.6, 31.8–97.9 and 112.2–710.0 μg/ml, respectively. The data were statistically analyzed by a two-factor analysis of variance (ANOVA). The first factor was time-of-day (8 levels), and the second one was the doses (4 levels including the control).

Figure 1 shows the changes in the body weight and fluid intake of rats during a long-term administration of nicotine. The changes in the body weight and fluid intake of control groups during this period were from 110.8 ±1.1 to 372.2±4.5 g and from 18.2±2.2 to 37.5±4.9 ml, respectively. At the dose of 0.5 mg/kg/day, no statistically significant difference in both fluid intake and weight gain was observed as compared with those in the water-treated control groups. However, nicotine suppressed the drinking at high doses. At doses of 5 and 20 mg/kg/day, the fluid intake was 20.0±2.1 and 5.7±1.8 ml, respectively, at the end of the nicotine treatment. As for weight gain, at the dose of 20
mg/kg/day, nicotine resulted in a marked repression of the weight gain in the rats. The changes in the weight gain of nicotine-treated groups were from 108.1 ±1.6 to 385.9±8.6 g (0.5 mg/kg/day), from 107.7 ±1.6 to 341.5±8.4 g (5 mg/kg/day) and from 104.6±1.9 to 215.2±14.6 g (20 mg/kg/day).

Figure 2 shows diurnal patterns of ambulatory activity and drinking. The data are expressed as mean total counts during 3 hr segments. Diurnal ambulatory activity and drinking patterns revealed two peaks characteristic to nocturnal animals in both the nicotine-treated and control groups. The basic diurnal patterns were not altered by a long-term oral administration of nicotine at all doses used in this study. However, the ambulatory activity was increased, and the drinking was suppressed by the nicotine treatment in a dose-dependent manner during the dark period. ANOVA revealed significant time-of-day, F(7,312)=75.34, P<0.001, and dose, F(3,312)=21.44, P<0.001, dependent changes in the ambulatory activity counts, and it revealed significant time-of-day, F(7,312)=150.38, P<0.001, and dose, F(3,312)=32.23, P<0.001, dependent changes in drinking counts.

In the present study, we used a long-term oral self-administration of nicotine, since it is fully possible that parenteral injection of nicotine might bring about stress to the experimental animals, and therefore, it would be difficult to see the naive behavior of these animals accurately. The present experiment demonstrated that nicotine suppressed the drinking behavior. A similar result was reported by Rowell et al. (1) that when nicotine solution (100 μg/ml) was orally administered to mice, fluid intake was drastically reduced and did not return to control levels. They suggested that taste aversion is an important factor in reducing fluid intake, since the addition of a small amount of sodium saccharin (2 μM) to the nicotine solutions led to an increase in the amount of fluid intake. On the other hand, the release of ADH through nicotine (10) may be concerned with this reduction in fluid intake of the orally nicotine-treated rats. However, an immediate interaction between the antidiuretic effects of ADH release and thirst regulation has not been demonstrated (11). Although no reports were available on the taste threshold for nicotine in rats, in the present study, the reduction of fluid intake at
high concentration of nicotine solutions might be associated with the taste and smell of nicotine solution.

In contrast to the decrease in the fluid intake, a long-term administration of nicotine induced a dose-dependent increase in the ambulatory activity. The effects of nicotine on spontaneous motor activity in rats have been reported by many investigators. However, there are few reports on the effects of free intake of nicotine solution on spontaneous motor activity for long-term periods (12). In regard to the effects of the light/dark condition in rats, Bovet et al. (7) reported that nicotine (0.2 and 1.0 mg/kg/day, s.c.) increased wheel-running activity during the light period, but decreased this behavior during the dark period. In addition, nicotine (1.0 mg/kg/day, s.c.) induced significant reduction of the distance effect during the dark period, although the effect was not so significant at a small dose of nicotine (0.2 mg/kg/day, s.c.). Thus, their result appeared to be in contrast to our present data showing a dose-dependent increase in the ambulatory activity during the dark period. The difference of these phenomena might be concerned with the distinct administration of nicotine, because the pharmacokinetic mechanism of nicotine would be expected to be quite different between oral administration and subcutaneous injection.

Some of the behavioral effects of nicotine resemble those of amphetamine (13–15), which is known to produce anorexia and adipsia through catecholaminergic alterations in the brain (16). It has been reported that nicotine may produce its hypophagic and hypodipsic effects through release of noradrenaline (11). The increase in the ambulatory activity by nicotine treatment might be related to amphetamine-like effects of the psychomotor facilitation. The different changes observed between the ambulatory activity and drinking at the doses of 5 and 20 mg/kg/day of nicotine may reflect the action of this drug via different central nervous systems.

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