Effects of Saiko-ka-ryukotsu-borei-to on spontaneous locomotor activity in mice

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Abstract: The effects of the Japanese Kampo (herbal) medicine, Saiko-ka-ryukotsu-borei-to, on spontaneous locomotor activity were studied in mice. Saiko-ka-ryukotsu-borei-to (60 mg, 150 mg and 300 mg/kg/day) was administered for 14 consecutive days in the drinking water and spontaneous locomotor activity was measured for 60 min by a photocell ambulometer. Saiko-ka-ryukotsu-borei-to (60 mg/kg/day) significantly increased the total activity count on the 11th day after the start of administration when compared to vehicle control, whereas failed to significantly affect the activity on the 2nd, 5th, 8th and 14th days. A similar significant increase was also found with a higher dose (150 mg/kg/day) on the 8th day after the start of administration. However, the highest dose (300 mg/kg/day) did not significantly affect locomotor activity throughout the experimental period. We have previously reported that Saiko-ka-ryukotsu-borei-to, at a dose of 60 mg/kg/day, enhances escape attempts assessed by water-wheel rotations in a mouse model of despair, particularly on the 8th, 11th and 14th days after the start of chronic treatment. However, at higher doses (150 and 300 mg/kg/day), Saiko-ka-ryukotsu-borei-to decreases the escaped attempts on the 5th and 8th days after the treatment. It is therefore concluded that the previously reported changes in escape attempts of mice are not associated with the changes in their spontaneous locomotor activity. (J. Oral Sci. 42, 157-161, 2000)

Key words: Saiko-ka-ryukotsu-borei-to, spontaneous locomotor activity, chronic administration, mouse.

Introduction

Several kinds of Japanese Kampo (herbal) medicines have been reported to possess psychotropic actions. Saiko agents, which contain Saiko (Bupleuri Radix) as one of their main ingredients, are the prescription of choice for patients who are in a state of depressive mood, because there are few incidences of side effects (1). In fact, such prescriptions have recently been introduced to Japanese dental clinics for the treatment of several psychosomatic diseases. We have recently found data using animal experiments suggesting that Saiko-ka-ryukotsu-borei-to, one of the Saiko agents, has both antidepressive and antinociceptive properties (2). In particular, at a dose of 60 mg/kg/day, it produces antidepressive effects similar to those of the prototype tricyclic antidepressant imipramine, on the basis of a mouse model of despair (2). It is well known, however, that drugs affecting motor behavior, such as amphetamines, also affect results from the behavioral despair model (3-5). Accordingly, the enhanced escape attempts found particularly on the 5th day after chronic treatment with Saiko-ka-ryukotsu-borei-to, as assessed by water-wheel rotation (2), could also have been a result of heightened spontaneous motor activity in the mice. Likewise, antinociceptive effects found on the 14th day after chronic treatment with Saiko-ka-ryukotsu-borei-to, as assessed by acetic acid-induced writhing (2), could also have been a result of reduced motor activity in the mice.

In the present study, we therefore examined whether...
chronic Saiko-ka-ryukotsu-borei-to treatment affects the motor activity of mice, thereby possibly influencing the results obtained from water-wheel rotation and acetic acid-induced writhing. For that purpose, spontaneous locomotor activity in mice administered chronically with Saiko-ka-ryukotsu-borei-to was measured by using a photocell ambulometer (Opto-Varimex) on the 2nd, 5th, 8th, 11th and 14th days after the start of chronic administration.

**Materials and Methods**

**Animals**

Male ddY mice (35-45 g) were housed in a temperature-controlled environment under a light (07:00-19:00 h)/dark (19:00-07:00 h) cycle with free access to food and water. Behavioral testing was performed between 10:00 h and 15:00 h.

**Behavioral methods**

For the measurement of spontaneous locomotor activity, mice were placed singly in experimental boxes (32 cm × 32 cm × 40 cm) with Perspex sides. Immediately after placement, locomotor activity was measured with a battery of infra-red photocells set 3 cm above the floor (Opto-Varimex, Columbus Instruments Ltd., Ohio, USA). The method of behavioral measurement employed in this study was based on a previously reported procedure (6). The number of beam interruptions during the 60-min observation period was automatically registered as locomotor activity on the 2nd, 5th, 8th, 11th and 14th days after commencing the chronic administration of Saiko-ka-ryukotsu-borei-to.

The experiments were performed in accordance with institutional guidelines on the care and use of experimental animals that are in compliance with the UK Animals (Scientific Procedures) Act, 1986, and all efforts were made to minimize animal suffering and to reduce the number of animals used.

**Drug**

Saiko-ka-ryukotsu-borei-to (containing 4.5 g powder extract prepared in boiling water for 60 min from a mixture of herbs: 5.0 g Bupleuri Radix, 4.0 g Pinelliae Tuber, 3.0 g Cinnamomi Cortex, 3.0 g Hoelen, 2.5 g Scutellariae Radix, 2.5 g Zizyphi Fructus, 2.5 g Ginseng Radix, 2.5 g Ostreae Testa, 2.5 g Fossilia Ossis Mastodi and 1.0 g Zingiberis Rhizoma), a Japanese Kampo medicine, was obtained from Tsumura Co. The Kampo medicine, in three different doses (60 mg, 150 mg and 300 mg powder extract/kg/day), was orally administered to mice for 14 consecutive days in drinking water.

**Statistical analysis**

All values are expressed as the mean ± S.E.M (n = 5-7). The total photocell counts in a 60-min observation period were compared to those of vehicle controls by one-way analysis of variance (ANOVA) followed by a post-hoc Dunnett's test. Differences were considered significant when p < 0.05.

**Results**

Immediately after their transfer to the observation boxes, the control animals, taking drinking water only, started to walk around to the walls (exploratory behavior). This locomotor activity decreased gradually till about 60 min after the transfer (Fig. 1), and the total photocell counts measured in a 60-min observation period of each trial day were found to be similar (Fig. 2).

The administration of Saiko-ka-ryukotsu-borei-to (60 mg/kg/day), when compared to the control condition, significantly increased locomotor activity on the 11th day after administration. Such an increase was not observed on the remaining trial days (Figs. 1 and 2). The administration of a higher dose (150 mg/kg/day) of Saiko-ka-ryukotsu-borei-to, compared to the control condition, also significantly increased locomotor activity on the 8th day after administration. However, there was no significant change in the locomotor activity on the remaining trial days (i.e. the 2nd, 5th, 11th and 14th days) (Figs. 1 and 2). Moreover, the administration of the highest dose (300 mg/kg/day) of Saiko-ka-ryukotsu-borei-to did not significantly affect the photocell counts at any trial days (Figs. 1 and 2).

**Discussion**

Previous studies, in which the same dose range (60-300 mg/kg/day) of Saiko-ka-ryukotsu-borei-to was employed, have suggested that Saiko-ka-ryukotsu-borei-to may have antidepressive and antinociceptive properties (2). In particular, the lowest dose (60 mg/kg/day) enhanced escape attempts as assessed by water-wheel rotations in a mouse model of despair on the 8th, 11th and 14th days after the start of chronic administration.

This enhancement was similar to that seen with the prototype tricyclic antidepressant, imipramine (2). This animal model of despair has been reported to be a better quantifying model (7) than the conventional Porsolt's forced-swimming test (3) that assesses immobilization of animals. It is well known, however, that drugs affecting motor behavior, such as amphetamines, also affect results from the behavioral despair model (3-5). The possibility that the enhanced escape attempts found on the 8th, 11th and 14th days after the chronic treatment of Saiko-ka-
ryukotsu-borei-to (2) was a result of the increased spontaneous motor activity of the mice cannot, therefore, be excluded. In this context, the reported antidepressive effects of Saiko-ka-ryukotsu-borei-to are still in need of further experimental support to corroborate the drugs antidepressive properties. Accordingly, this study examined the effects of chronic Saiko-ka-ryukotsu-borei-to administration on spontaneous locomotor activity in order to investigate the possible influence on water-wheel rotation results.

The results of this study clearly demonstrated that the chronic administration of Saiko-ka-ryukotsu-borei-to (60
mg/kg/day) to mice did not significantly alter locomotor activity on the 8th and 14th days after the treatment, though a significant enhancement was found on the 11th day. Moreover, at a higher dose (150 mg/kg/day), spontaneous locomotor activity was increased on the 8th day after the treatment, during the same period Saiko-ka-ryukotsu-borei-to not only failed to enhance the number of water-wheel rotations, but actually decreased their frequency (2). These findings of the present and previous studies (2) strongly suggest a lack of correlation between spontaneous locomotor activity and water-wheel rotations, at least with regard to the effects of chronic Saiko-ka-ryukotsu-borei-to administration. Thus, these results together provide experimental support to the assumption that the previously reported enhancement of escape attempts (2) was not due to increased spontaneous locomotor activity.

Likewise, the antinociceptive effects found in mice on the 14th day after chronic treatment with Saiko-ka-ryukotsu-borei-to (60 mg, 150 mg and 300 mg/kg/day), as assessed by a reduction in acetic acid-induced writhing (2), could have been a result of reduced motor activity produced by Saiko-ka-ryukotsu-borei-to, presumably via hypnotic and/or muscle relaxant actions. However, in the present study, no significant reduction in spontaneous locomotor activity was evident from chronic Saiko-ka-ryukotsu-borei-to administration. A lack of correlation between spontaneous locomotor activity and acetic acid-induced writhing again provides experimental support for the assumption that the previously reported reduction of acetic acid-induced writhing (2) was not due to reduced spontaneous locomotor activity.

As is often seen with the Kampo medicines, Saiko-ka-ryukotsu-borei-to did not show dose-dependency in its effects on spontaneous motor activity. Since only the lowest dose (60 mg/kg/day) of Saiko-ka-ryukotsu-borei-to, which is close to its clinical dose, has been shown to possess both antidepressive and antinociceptive properties (2), it is important to select the right clinical dose. This is particularly true in a sense that Kampo medicines have a significant clinical benefit in treating psychosomatic diseases in the dental field, which are usually somehow related to pain.

In conclusion, the present study provides experimental evidence against the objection that the previously reported increase in water-wheel rotation in a mouse model of despair and decreased number of acetic acid-induced writhing in mice by chronic Saiko-ka-ryukotsu-borei-to administer.
administration, might be a result of an alteration in motor behavior of the mice.

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References