Effects of Hochu-ekki-to on spontaneous locomotor activity in mice

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I. INTRODUCTION

Several kinds of traditional Chinese herbal (Kampo) medicines have been reported to possess psychotropic actions (1). 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 anxiety or depressive mood because of the rarity of side effects (1). Such prescriptions have recently been introduced to the dental clinic for the treatment of several psychosomatic diseases. We have recently reported that Hochu-ekki-to, one of the Saiko agents, possesses antidepressive properties 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 for behavioral despair (3-5). Accordingly, the enhanced escape attempts found particularly on the 11th and the 14th days after chronic treatment with Hochu-ekki-to, as assessed by water-wheel rotations (2), could also have been a result of heightened spontaneous motor activity in the mice. In the present study, it was therefore decided to examine whether chronic Hochu-ekki-to treatment affects the motor activity of mice, thereby possibly...
influencing the results obtained from water-wheel rotation.

II. MATERIALS AND METHODS

Animals

Male ddY mice (35-45g) 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 (32cm × 32cm × 40cm) with Perspex sides. Immediately after placement, locomotor activity was measured with a battery of infra-red photo-cells set 3cm above the floor (Opto-Varimex, Columbus Instruments Ltd.). The method of behavioral measurement employed in this study was based on the one reported previously (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 Hochu-ekki-to.

Drug

Hochu-ekki-to (containing 5.0g powder extract prepared in boiling water for 60min from a mixture of herbs: 4.0g Astragali Radix, 4.0g Atractylodis Lanceae Rhizoma, 4.0g Ginseng Radix, 3.0g Angelicae Radix, 2.0g Bupleuri Radix, 2.0g Zizyphi Fructus, 2.0g Aurantii Nobilis Pericarpium, 1.5g Glycyrrhizae Radix, 1.0g Cimicifugae Rhizoma and 0.5g Zingiberis Rhizoma) was obtained from Tsumura and administered orally (60mg, 150mg and 300mg powder extract/kg/day) for 14 consecutive days in drinking water.

Statistical analysis

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

III. RESULTS

Immediately after their transfer to the observation boxes, the control animals started to walk around the walls (exploratory behavior). This locomotor activity fell rapidly till about 30min after the transfer and fell gradually thereafter (Fig. 1).

The administration of Hochu-ekki-to (60mg/kg/day), compared to the control, tended to reduce the photo-cell count on the second day after administration, increased the counts on the 5th and the 8th days and then produced the same count as the control level on the 11th and 14th days (Figs. 1 and 2). Higher doses (150 and 300mg/kg/day) of Hochu-ekki-to produced a similar time-dependent change in the photo-cell count, though the effect was not dose-dependent (Fig. 2).

IV. DISCUSSION

Previous studies in which the same dose range (60-300mg/kg/day) of Hochu-ekki-to was employed have
Fig. 1 Effects of Hochu-ekki-to (60, 150 and 300mg/kg/day) on spontaneous locomotor activity in mice. The trials of 60 min each were carried out on the 2nd, 5th, 8th, 11th and 14th days after the start of administration. The drug was administered orally for 14 consecutive days in drinking water. The data were expressed as mean (± S.E.M., n= 5 - 7) numbers of beam interruptions counted in consecutive 5-min observation periods for 60 min.
shown that Hochu-ekki-to possesses antidepressive (2) and antinociceptive (7) properties. In particular, it enhanced escape attempts as assessed by water-wheel rotations in a mouse model of despair on the 11th and the 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 (8) than Porsolt's forced swimming test (3). It is well known, however, that the drugs which affect motor behavior, such as amphetamines, also affect results for behavioral despair (3-5). The possibility that the enhanced escape attempts found on the 11th and the 14th days after the chronic treatment of Hochu-ekki-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 Hochu-ekki-to are still in need of further experimental support to corroborate the drugs antidepressive properties. This study accordingly examined the effects of chronic Hochu-ekki-to administration on locomotor activity in order to investigate the possible influence on water-wheel rotation results.

The results of this study clearly showed that the chronic administration of Hochu-ekki-to to mice did not significantly alter locomotor activity on the 11th and 14th days after the treatment. These results provide experimental support to the assumption that the previously reported enhancement of escape attempts (2) was not due to increased spontaneous locomotor activity. In contrast, spontaneous locomotor activity was increased on the 5th and 8th days after the treatment; during the period in which Hochu-ekki-to failed to increase the number of water-wheel rotations (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 Hochu-ekki-to administration.

The increase in locomotor activity, especially on the 5th and 8th days after the start of Hochu-ekki-to administration, is of much interest, because the drug was originally used to replenish vital energy for the management of physical exhaustion. The increased locomotor activity observed on the 5th and 8th days after the treatment returned to normal from the 11th day. This suggests the use of clinical
administration periods of about one week for treating physical and two weeks for psychological exhaustion. As is often seen with the Kampo medicines, Hochu-ekki-to, at least in the dose range employed in this study, did not show dose-dependency in its effects on spontaneous motor activity. This may also suggest the importance of selecting the right clinical dosage.

In conclusion, this study provides experimental evidence against the objection that the previously reported increase in water-wheel rotations in a mouse model of despair, found on the 11th and 14th days after the start of chronic Hochu-ekki-to administration, might be a record of reflex motor behavior. The present study also suggests significant points for the potential clinical use of Hochu-ekki-to as an antidepressant.

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REFERENCES