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# Effects of 24-Hr Fasting on Methamphetamine- and Apomorphine-Induced Locomotor Activities, and on Monoamine Metabolism in Mouse Corpus Striatum and Nucleus Accumbens

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ITOH, T., S. MURAI, H. NAGAHAMA, H. MIYATE, E. ABE, H. FUJIWARA AND Y. SAITO. *Effects of 24-hr fasting on methamphetamine- and apomorphine-induced locomotor activities, and on monoamine metabolism in mouse corpus striatum and nucleus accumbens*. PHARMACOL BIOCHEM BEHAV **35**(2) 391–396, 1990.—The effects of 24-hr fasting on the vertical (VMA) and horizontal (HMA) locomotor activities, on cage climbing activity and on brain monoamine-related substances, were examined using male ddY mice. Both the VMA and HMA increased with fasting, but not the cage climbing activity. Methamphetamine (2 mg/kg, SC) increased the VMA and HMA in both the feeding and fasting mice, whereas with apomorphine (0.1 mg/kg, SC) both decreased. Furthermore, pretreatment with haloperidol (0.025 mg/kg, SC) showed no influence on the methamphetamine-induced VMA increase in both the feeding and fasting mice. However, pretreatment with haloperidol inhibited the methamphetamine-induced HMA increase in both the feeding and fasting mice and showed a higher level of HMA in fasting mice than in feeding mice. When measuring brain monoamine-related substances, the DA, NE, 5-HT, and 5-HIAA levels in the corpus striatum increased, whereas the 3-MT level decreased. The monoamine levels in the nucleus accumbens of fasting mice were the same as those in feeding mice, except for a decrease of the 3-MT level. These results suggest that the locomotor activity in fasting mice may be increased by a change in the sensitivity of dopaminergic neurons in the corpus striatum.

Fasting Methamphetamine Apomorphine Haloperidol Vertical and horizontal locomotion Monoamine Mouse

REPEATED administration of psychomotor stimulants, such as amphetamine (29,30) and apomorphine (4), produces changes in the behavior of mice and rats. However, it is known that such behavior may be modified by fasting (9,34). Furthermore, there are some reports with regard to the influence of fasting on the monoamine levels in mouse and rat brains: namely, 1) stimulation of serotonin metabolism in the rat brain (6, 19, 23, 32); 2) inhibition of norepinephrine metabolism in the rat hypothalamus (18,28); 3) increase in the dopamine level in the rat amygdala, while at the same time a decrease of the norepinephrine and dopamine levels in the rat hypothalamus (31); and 4) increase of the homovanillic acid level in the corpus striatum, but not the dopamine level (10,11). These studies provide evidence that fasting exerts an influence on locomotion (2, 9, 22, 34), and on the metabolism and synthesis of monoamines in the brain. However, variations in the brain monoamine levels due to fasting vary, depending on the investigator. Furthermore, the connection between fasting and function of the central nervous system is not clear, although fasting has been thought to be closely related to its behavior.

Therefore, in order to clarify, from a behavioral point of view, whether or not fasting exerts any influence on the central nervous system in mice, the effects of 24-hr fasting on locomotor activity and on the monoamine levels in the corpus striatum and nucleus accumbens were examined.

## METHOD

### *Animals*

Animals used in the experiment were male ddY mice, 4 weeks old, weighing 18–22 g, purchased from the Shizuoka Experimental Animal Agriculture Co. (Japan). The mice were housed in a stainless wire cage (26 W × 38 D × 17 H, cm), ten per cage, for 2 weeks with food and water ad lib, maintained in a room under a

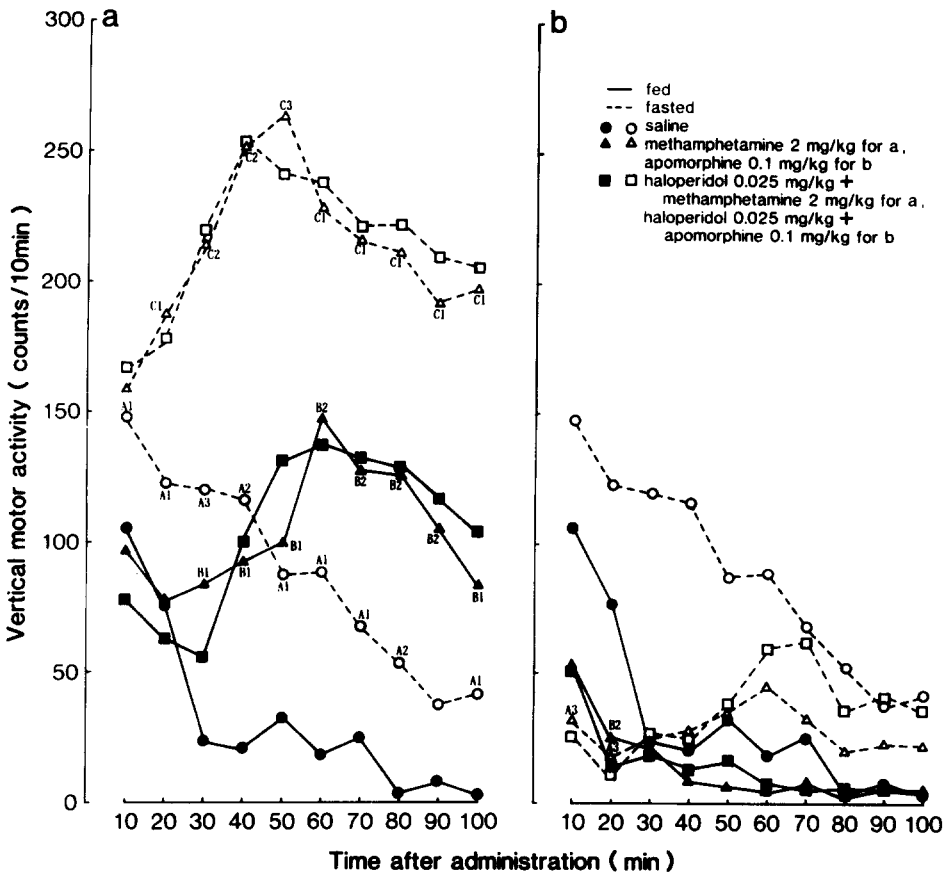


FIG. 1. Effects of 24-hr fasting on the vertical motor activity of methamphetamine (a) and apomorphine (b) in saline or haloperidol-pretreated mice. (A and B) Differ significantly from mice which were fed. (C) Differs significantly from fasting mice. Numerals of one, two and three on A, B, and C indicate significant difference from each group, $p<0.05$, $p<0.01$ and $p<0.001$, respectively. Each point is expressed as mean value obtained from 10 mice.

12-hr light-dark cycle (light, 7:00–19:00; dark, 19:00–7:00), with an ambient temperature of 22–26°C, and a humidity of 55–65%.

When six weeks old, the mice were divided into two groups: one group, housed with food and water ad lib (feeding); and the other group, housed without food and water for 24 hr (fasting).

*Locomotor Activity*

*Vertical (VMA) and horizontal (HMA) locomotor activities.* The locomotor activity of the mice was measured between 9 a.m. and 1 p.m. using 10 sets of apparatus developed by the authors (14). The apparatus can divide the activity of each mouse into VMA and HMA, and measure the activities of many mice at the same time. The apparatus consists of a plastic box (16 W × 29 D × 30 H, cm). An infrared photo-coupler was mounted at a height of 1.8 cm to measure the HMA and nine infrared photo-couplers were mounted at a height of 6.5 cm to measure the VMA.

Feeding and fasting mice were first placed in the box to acquaint them to their surroundings for 10 min. Then, after injecting drugs subcutaneously, their activity was measured for 100 min.

*Cage climbing activity.* Cage climbing activity of both the feeding and fasting mice was measured using 20 sets of a modified type of apparatus made of steel wire (26). Briefly, the apparatus is a cylindrical cage have a diameter of 12 cm and a height of 14 cm, with steel wire (diameter, 2 mm) set at 1 cm intervals. The mice were placed in the cage to acquaint them to their surroundings for 90 min.

Then, after subcutaneously injecting apomorphine at 1 mg/kg, their cage climbing activity was measured for 90 min. The activity was evaluated as follows: 0: touching the floor with fore- and hind-paws, 1: gripping the steel wire with fore paws, 2: gripping the steel wire with fore- and hind-paws, 3: gripping the steel wire with fore- and hind-paws for more than 5 min.

*Brain Monoamine-Related Substances*

The mice were killed by immersing into dry ice ethanol solution to minimize the postmortem changes of monoamine metabolites in the brain, after which the brain was removed. The corpus striatum and nucleus accumbens were isolated from the nearly frozen brain, placed on a cooled glass plate according to a modification of the conventional method (12), then weighed and stored at −80°C until assay. The content of the monoamine-related substances was measured by our method (21) using high-performance liquid chromatography coupled with electrochemical detection (HPLC-ECD). The frozen tissues were homogenized with an Ultrasonic Cell Disruptor (Model 200, Branson,

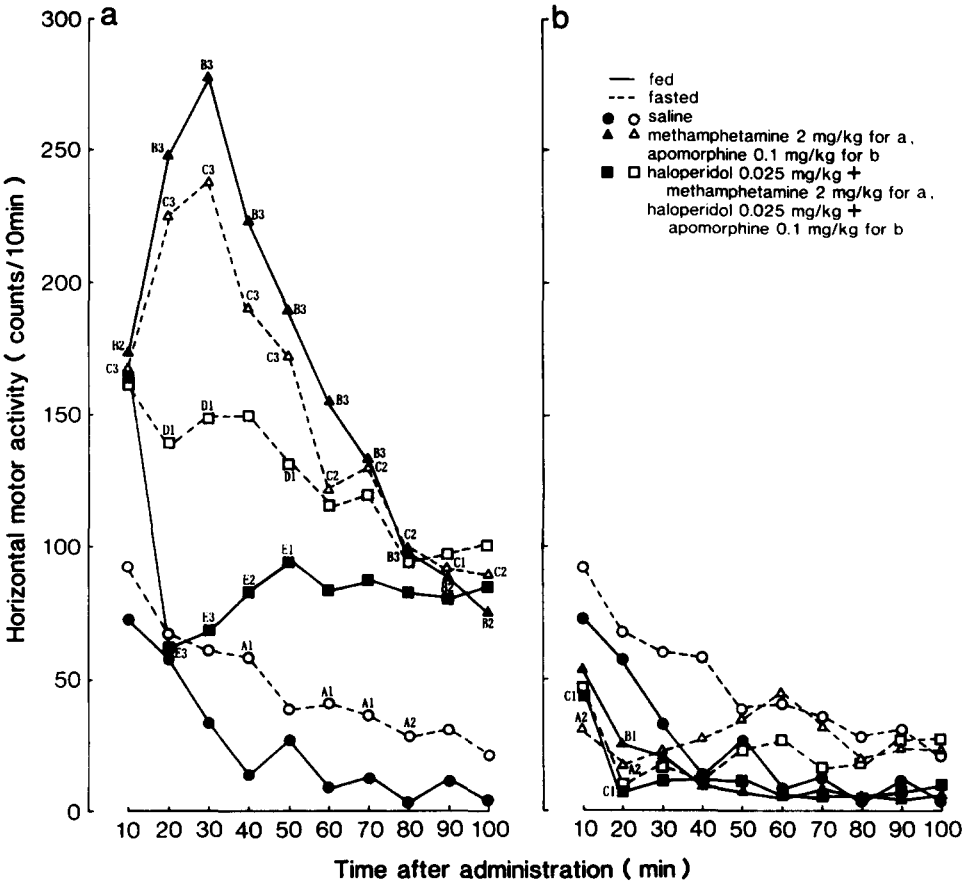


FIG. 2. Effect of 24-hr fasting on the horizontal motor activity of methamphetamine (a) and apomorphine (b) in saline or haloperidol-pretreated mice. (A and B) Differ significantly from mice which were fed. (C, D and E) Differ significantly from fasting mice, fasting mice treated with methamphetamine and fasting mice treated with haloperidol + methamphetamine, respectively. See legend in Fig. 1 for the numerals on A, B, C, D and E.

TABLE 1

CONCENTRATION OF MONOAMINE-RELATED SUBSTANCES IN DISCRETE BRAIN AREAS OF FEEDING AND FASTING MICE

| | Corpus Striatum | | Nucleus Accumbens | |
|---|---|---|---|---|
| Compounds | Feeding | Fasting | Feeding | Fasting |
| Tyr | 7786 ± 1562 | 8889 ± 818 | 11835 ± 1985 | 13283 ± 1534 |
| DA | 10873 ± 851 | 12035 ± 584* | 7434 ± 872 | 7716 ± 1109 |
| DOPAC | 636 ± 55 | 695 ± 49 | 1049 ± 122 | 946 ± 130 |
| HVA | 1061 ± 98 | 1139 ± 128 | 683 ± 57 | 778 ± 89 |
| 3-MT | 219 ± 34 | 178 ± 18* | 129 ± 14 | 102 ± 18* |
| NE | 51 ± 8 | 84 ± 16† | 546 ± 47 | 599 ± 88 |
| MHPG | 42 ± 3 | 43 ± 3 | 141 ± 16 | 135 ± 19 |
| Trp | 3131 ± 274 | 3436 ± 358 | 6862 ± 920 | 7265 ± 381 |
| 5-HT | 428 ± 54 | 496 ± 358* | 720 ± 98 | 761 ± 127 |
| 5-HIAA | 345 ± 39 | 467 ± 44† | 394 ± 39 | 425 ± 55 |

The values are expressed as the mean ± S.D. (ng/g wet tissue weight) for six mice. * and †: significantly different from feeding mice, $p<0.05$ and $p<0.01$, respectively.

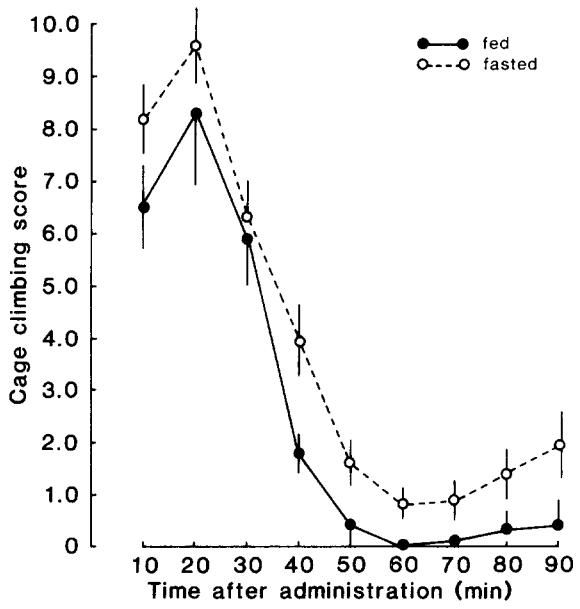


FIG. 3. Cage climbing activity in mice given apomorphine (1 mg/kg). Vertical bars represent S.E. of mean obtained from 10 mice.

CT) in a 0.1 M perchloric acid solution. Homogenates were centrifuged at 12,000 × g for 10 min at 4°C and the supernatants decanted and filtered through a 0.45 μg filter. The clear supernatant was injected into the HPLC-ECD system. The HPLC-ECD system consisted of a delivery pump (L-5,000, Yanagimoto, Japan), and an analytical column (EICOMPAK, MA-ODS, 250 × 4.6 mm i.d., Eicom). The electrochemical detector (VMD-501, Yanagimoto, Japan) with a graphite electrode (WE-3G, Eicom) was used at a voltage setting of +0.83 V versus an Ag/AgCl reference electrode. The mobile phase consisted of 0.02 M sodium acetate/0.0125 citric acid buffer (pH 3.92), containing 16% methanol and 0.033% heptansulfonic acid.

### *Drugs*

Methamphetamine (Dainippon Pharmaceutical Co., Japan) 2 mg/kg; apomorphine HCl (Sigma Chemical Co., USA) 0.1 and 1 mg/kg; haloperidol (Shionogi Pharmaceuticals, Japan) 0.025 mg/kg were used in the experiment. The drugs were dissolved in a physiological saline solution, and administered subcutaneously at a volume of 0.05 ml/10 g body weight. Haloperidol was first dissolved in 0.1 M tartaric acid at the rate of a mg/ml, then was further dissolved in a physiological saline solution. An extremely small amount of ascorbic acid was added to the apomorphine solution.

### *Statistics*

The statistical significance of the data obtained was analyzed with the Mann-Whitney U-test and the Student *t*-test.

## RESULTS

### *Methamphetamine- and Apomorphine-Induced VMA and Fasting*

The VMA of fasting mice increased significantly over that of feeding mice, as shown in Fig. 1. Methamphetamine increased the VMA in both the feeding and fasting mice, with a significantly higher level of VMA in the fasting mice. Haloperidol pretreatment of both the feeding and fasting mice exerted no influence on the increased VMA induced by methamphetamine. On the other hand, apomorphine inhibited the VMA in both the feeding and fasting mice. However, haloperidol pretreatment of both the feeding and fasting mice exerted no influence on the inhibitory effect of apomorphine. These results show that the dosage of haloperidol used in the present study (0.025 mg/kg) exerts no influence on the effect that methamphetamine and apomorphine have on the VMA.

### *Methamphetamine- and Apomorphine-Induced HMA and Fasting*

The HMA of fasting mice, about 40 min after beginning measurement, showed a significant increase over that of feeding mice, as shown in Fig. 2. Although with methamphetamine there was a tendency to a higher level of HMA in the feeding mice than in the fasting mice, no statistical difference in the HMAs of either the feeding or the fasting mice was recognized. However, haloperidol pretreatment of both the feeding and fasting mice significantly inhibited the methamphetamine-induced HMA increases, which were more than in those not pretreated with haloperidol, and which showed a higher level of HMA in fasting mice than in feeding mice. On the other hand, apomorphine inhibited the HMA in both the feeding and fasting mice, regardless of whether or not they were pretreated with haloperidol. These results show that the dosage of haloperidol used in the present study had an influence on the methamphetamine-induced HMA, but not on the apomorphine-induced HMA.

### *Apomorphine-Induced Cage Climbing Activity and Fasting*

Cage climbing activity induced by the administration of apomorphine at 1 mg/kg to fasting mice, as shown in Fig. 3, showed a tendency to increase when compared to that of the feeding mice, but the levels between the activities in the feeding and fasting mice showed no statistical difference. This indicates that 24-hr fasting exerts no influence on cage climbing activity, which has been thought to reflect a functional change in mouse corpus striatum postsynaptic DA receptors.

### *Monoamine-Related Substances in Discrete Mouse Corpus Striatum and Nucleus Accumbens and Fasting*

*Corpus striatum.* The DA level in fasting mice, as shown in Table 1, was significantly higher than that of feeding mice. However, the HVA level and the DOPAC, metabolized from DA, were the same as those in the feeding mice, although a significantly lower level of 3-MT was noted in the fasting mice. The NE level in fasting mice was significantly higher compared to that in feeding mice, but the level of MHPG metabolized from NE was equal to that in the feeding mice. The 5-HT and 5-HIAA levels in fasting mice were significantly higher than those in feeding mice.

*Nucleus accumbens.* All levels of monoamine-related substances measured in the present study (see Table 1) were approximately the same in both the feeding and fasting mice, except for a significant decrease of the 3-MT level in fasting mice.

## DISCUSSION

The present results showed an increase in locomotor activity in fasting mice: the VMA and HMA agreed with earlier reports (2, 13, 22) and methamphetamine markedly increased the VMA and HMA in both the feeding and fasting mice. It is known that the enhancement of locomotor activity induced by amphetamine or methamphetamine develop as a result of interaction between the stereotypy produced by the stimulation of dopaminergic neurons in the corpus striatum (8), and the locomotion produced by stimulation of dopaminergic neurons in the nucleus accumbens (27,33). Thus, it is supposed that the increase of locomotor activity induced

by amphetamine or methamphetamine further increases when pretreated with a small dose of haloperidol, which inhibits the development of stereotypy induced by amphetamine or methamphetamine (9).

We advanced this study with a conception based on the assumption that a low dose of methamphetamine increases locomotion and also develops a low level stereotyped behavior at the same time. However, in the present study, it was difficult to determine the stereotyped behavior from the VMA and HMA because that is contained within the mode of their locomotions. Although the VMA and HMA increased in all mice as a result of methamphetamine, the VMA and HMA patterns clearly differed from each other. However, pretreatment with a small dose of haloperidol did not cause a further increase of the VMA in either the feeding or the fasting mice, whereas the HMA increase with methamphetamine was inhibited by pretreatment with a small dose of haloperidol in both the feeding and fasting mice, showing a higher level of HMA in fasting mice than in feeding mice. These do not agree with an earlier report (9) which showed an accelerating effect of amphetamine on the locomotor activity in the feeding and fasting mice pretreated with haloperidol.

The difference in effects of methamphetamine on the VMA and HMA is similar to the difference in degree of severity of stereotypy observed in fasting rats and reported earlier (5,9), and also similar to the difference in the effects of amphetamine on the rearing behavior and locomotor activity in rats of an earlier report (3). It is known that stereotyped behavior produced by amphetamine develops as a result of functional stimulation of the DA receptors in the corpus striatum (8), and that fasting suppresses the development of stereotypy (9). Thus, because the increased VMA along with methamphetamine further increases by fasting, but is not inhibited by pretreatment with haloperidol which inhibits the development of stereotypy, it is suggested that the increase of VMA resulting from fasting may be due to the change of sensitivity to the DA receptors in the corpus striatum. Although stereotyped behavior in mice has been thought to be inhibited by fasting or treating with haloperidol, the mode of action in these inhibition differs from each other.

Subsequently, it is well documented that a low dose of apomorphine acts on the presynaptic DA receptors in the corpus striatum, and lowers the locomotor activity (4, 16, 20). In the present study, a low dose of apomorphine lowered the levels of both VMA and HMA in fasting mice to the same degree as in feeding mice, and the degree of the lowered levels were similar to the levels of VMA and HMA suppressed by a low dose of apomorphine in the feeding and fasting mice pretreated with a small dose of haloperidol.

Furthermore, cage climbing activity has also been used as a parameter for evaluating the hyperactivity of the postsynaptic DA receptors in the corpus striatum of mice (26). In the present study, the cage climbing activity level in fasting mice was identical to that in feeding mice. This is in agreement with an earlier report (9) which showed that fasting had exerted no influence on the sensitivity to the postsynaptic DA receptors in the mouse corpus striatum. Thus, we surmise that an increase of locomotor activity in fasting mice may be induced by a change in the sensitivity of the presynaptic DA receptors which participate in the inhibition of the dopaminergic neurons in the corpus striatum and the development of stereotypy. Moreover, it is suspected that activity of dopaminergic neurons in the corpus striatum and in the nucleus accumbens is reflected in the VMA and HMA, but this has not yet been proven.

When measuring monoamine-related substances in the discrete mouse brain, an increase in the DA level, no change in the DOPAC and HVA levels, a decrease in the 3-MT level and an increase in the corpus striatum NE level of fasting mice was observed. This suggests that fasting may facilitate biosynthesis of DA and NE. However, our results did not agree with earlier reports (9–11), which showed no change in the DA and DOPAC levels and an increase in the HVA level in the corpus striatum of fasting mice. Furthermore, the levels of all the monoamines measured in the nucleus accumbens of fasting mice were no different from those in feeding mice, except for showing a low level of 3-MT in the nucleus accumbens. Although the decrease of the TYR level (24,28) and the increase of the TRP level (6, 19, 23, 32) in fasting mouse and rat brains have been reported, in the present study the TYR and TRP levels in fasting mice were no different from those in feeding mice.

It has been reported that an increase in locomotor activity induced by a moderate dose of apomorphine is related not only to the increased activity of the postsynaptic DA receptors in the corpus striatum (1,7), but also in the nucleus accumbens (15, 17, 33). Because a decrease of the 3-MT level, which is thought to reflect the level of released DA (36), is found in the corpus striatum and nucleus accumbens of fasting mice, fasting seems to inhibit a release of DA at the presynaptic sites in such areas. Therefore, these findings lead to provide the hypothesis that fasting induces a change in the sensitivity to the dopaminergic neurons, especially in the presynaptic DA receptors, in the corpus striatum and nucleus accumbens of mice. Thus, we persist that a further increase in locomotion due to fasting will develop as a result of a decrease in stereotyped behavior, which is related to the reduction of the DA release (a decrease in the 3-MT level) induced by fasting and the change of the sensitivity to the presynaptic DA receptors in the dopaminergic neurons of the mouse brain areas. This is also supported by the fact that fasting enhances the VMA and HMA as described above.

Moreover, the increase of 5-HT and 5-HIAA levels in the corpus striatum of fasting mice is in agreement with the results of earlier reports (6, 19, 23, 32). As there is a report that the stimulation of serotonergic neurons inhibits the amphetamine induced stereotyped behavior in rats (35), inhibition of dopaminergic neurons in the corpus striatum of fasting mice is also thought to induce stimulation of the 5-HT turnover. However, the influence of fasting on the central nervous system in mice is not yet fully understood; it needs further study.

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