Suppression of behavioral activity and hippocampal adrenaline caused by surgical stress in type 2 diabetes model mice

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Abstract

Background In these days, the occurrence of neuropsychological complications during perioperative period has become the subject of discussion. Diabetes is indicated as one of the metabolic risk factors. Although the number of patients with diabetes mellitus (DM) has been increasing, the pathophysiology of postoperative neuropsychological dysfunction in DM patient is still unclear. Recently, a deficiency of neurotransmitters, such as monoamines, was reported to be associated with mental disorders. Therefore, we investigated the effects of surgical stress on behavioral activity and the hippocampal noradrenaline (NA) level in type 2 diabetes mellitus model (T2DM) mice.Methods Eighty-four 6-week-old male C57BL/6J mice were divided into four groups (control, surgery control, T2DM, and surgery T2DM groups). T2DM mice were established by feeding a high fat diet (HFD) for 8 weeks. At 14 weeks of age, fifteen mice in every group underwent a series of behavioral tests including an open field (OF) test, a novel objective recognition (NOR) test and a light-dark box (LD) test. In the surgery groups, open abdominal surgery with manipulation of intestine was performed 24 hours before the behavioral tests as a surgical stress. Hippocampal NA level was examined in six mice in each group by high-performance liquid chromatography. The data were analyzed by Mann-Whitney U test and P values less than 0.05 were considered significant.Results The T2DM group showed significantly increased explorative activity in the NOR test (P = 0.0016) and significantly increased transition in the LD test (P = 0.043) compared with those in the control group before surgery. In T2DM mice, surgical stress resulted in decreased total distance in the OF test, decreased explorative activity in the NOR test, and decreased transition in the LD test (OF: P = 0.015, NOR: P = 0.009, LD: P = 0.007) and decreased hippocampal NA (P = 0.015), although they were not revealed in control mice.Conclusion T2DM mice by feeding a HFD showed increased behavioral activities, and surgical stress in T2DM mice caused postoperative hypoactivity and reduction of hippocampal NA level.

Background

In these days, the occurrence of neuropsychological complications during perioperative period have been discussed. The risk factors such as obesity, diabetes, dyslipidemia were indicated [1]. The number of people with diabetes mellitus (DM) has increased to about 425 million [2] and over 90% of those people have type 2 diabetes mellitus (T2DM) caused by diet and lifestyle [3]. In the early postoperative period, the cognitive outcome is worse in DM patients than in non-diabetic patients [4], and transient advanced mental impairment occurs more frequently in DM patients after aortic surgery [5]. Moreover, T2DM is also well known as one of the risk factors for postoperative delirium [6-8]. However, in DM patients, the pathophysiology of neuropsychological disorder and postoperative behavioral alteration has been unclear. Considering that the number of DM patients undergoing surgery will continue to increase, it is important to investigate the neuropsychological effect of surgical stress in DM patients.

Recently, it has been reported that monoamine as a neurotransmitter plays very important roles in arousal, cognitive activity and emotional activity [9]. Dysfunction of the monoamine system was shown to be associated with mental illnesses including depression [10], affective disorder [11] and anxiety

disorder [12]. From a psychopathological point of view, we hypothesized that neurotransmitter deficiency is associated with postoperative behavioral alterations and mental impairment in DM patients.

In the monoamine system, noradrenaline (NA) is associated with responses to stressful events and to be activated in an unexpected condition [9]. The locus caeruleus projection of NA to the cortex and hippocampus is thought to be strongly involved in modulation of attention [13]. In animal model, an increase of the hippocampal NA signal was reported to be associated with neuronal plasticity [14], synaptic plasticity [15], and memory retrieval [16], while a decrease of hippocampal NA levels is related to anxiety [17], depression [18] and hypoactivity [19]. However, the influence of acute surgical stress on the hippocampal NA system is not known.

Therefore, we focused on the behavioral alterations and hippocampal NA during the perioperative period in the state of DM. We used adult mice in which T2DM was induced by feeding a high fat diet (HFD) [20] in order to evaluate the influence of perioperative behavioral alterations. The purpose of this study was to clarify the impact surgical stress has on postoperative behavioral activity and hippocampal NA in T2DM model mice.

Results

Mild chronic hyperglycemia in T2DM mice

A graph of body weight gain is shown in Fig. 2(a). After 8 weeks of intervention with an HFD, body weight in the T2DM group was significantly increased compared with that in the control group ($n = 12$ per group, $P < 0.0001$). Changes in the levels of fasting blood glucose are shown in Fig. 2(b). Fasting blood glucose level in the T2DM group was significantly higher than that in the control group ($n = 12$ per group, $P<0.0001$).

The results of IPGTTs performed at 13 weeks of age are shown in Fig. 2(c). The glucose level in the T2DM group was significantly higher than that in the control group and prolonged hyperglycemia was observed in the T2DM group ($n = 12$ per group, $P < 0.0001$), indicating that the glucose intolerance was caused by feeding an HFD. The level of HbA1c in the T2DM group was also significantly higher than that in the control group ($n = 10$ per group, $P = 0.009$) as shown in Fig. 2(d). This result showed that mild chronic hyperglycemia was sustained in the T2DM model mice.

Hyperactive behaviors of T2DM mice

At 14 weeks of age, a series of behavioral tests was performed. The results of OF tests for evaluation of spontaneous locomotor activity and anxiety-like behaviors are shown in Fig. 3(a)(b). There were no differences in the total distance and time spent in the center in the OF test between the control group and the T2DM group. NOR tests were performed to evaluate explorative activity and cognitive function. Total explorative times during the familiarization phase of the NOR tests are shown in Fig. 4(a). The time spent for explorative activity was significantly longer in the T2DM group than in the control group ($P = 0.001$).

In the testing phase, there was no difference in the discrimination index between the T2DM group and the control group as shown in Fig. 4(b), and cognitive dysfunction was therefore not revealed in this experiment. LD tests were performed to examine explorative activity and anxiety. The frequency of transition between the light and dark chambers was significantly higher in the T2DM group than in the control group (P = 0.043) as shown in Fig. 5(a). However, the time spend in the light chamber was not different between the control group and the T2DM group as shown in Fig. 5(b).

Decrease of postoperative activity in T2DM mice caused by surgical stress

To evaluate postoperative behavioral alterations, the same series of behavioral tests was performed 24 hours after open abdominal surgery in both the surgery control group and surgery T2DM group. The total distance significantly decreased after surgery in T2DM mice (Fig. 3(a), P = 0.015) but not in the control mice. The time spent in the center significantly decreased in both the control mice and T2DM mice after surgery (Fig. 3(b), control vs surgery control: P = 0.006, T2DM vs surgery T2DM: P = 0.006), indicating that anxiety-like behavior was caused by surgical stress in both the control mice and the T2DM mice. In the familiarization phase of the NOR test, the total explorative time markedly decreased after surgery in T2DM mice (Fig. 4(a), P = 0.009) but not in control mice (P = 0.802). In the testing phase, there was no difference in the discrimination index between the control mice and T2DM mice during the perioperative period (Fig. 4(b)), and cognitive dysfunction was therefore not revealed either the control mice or T2DM mice after surgery. In the LD test, the frequency of transition of between the light and dark chambers was significantly reduced after surgery in T2DM mice (Fig. 5(a), P = 0.007). Surgical stress did not affect the time spent in the light chamber for either the control mice or T2DM mice (Fig. 5(b)).

Decrease of hippocampal NA induced by surgical stress in T2DM mice

HPLC analysis was performed to examine the hippocampal NA level. There was no difference in the hippocampal NA level between the control group and T2DM group (Fig. 6, P = 0.937). However, in T2DM mice, the hippocampal NA level was significantly reduced after surgery (P = 0.015), while there was no difference in the control mice (control vs surgery control, P = 0.485).

Discussion

In the present study, T2DM model mice fed an HFD for 8 weeks showed an increase of explorative activity in the NOR test and more frequent transition in the LD test. We also found that surgical stress in T2DM model mice caused a decrease of postoperative activity in all of the behavioral tests and a decline in hippocampal NA level. These findings indicate that T2DM causes behavioral alterations and that surgical stress under a chronic diabetic condition induces postoperative behavioral changes and has an influence on the release of neurotransmitters in the brain. And, this might be associated with perioperative neuropsychological complications in diabetic patients.

In our experiment, we used 14-week-old adult male mice after feeding an HFD for 8 weeks and we performed NOR, LD and OF tests for perioperative behavioral assessment. Before the operation, we found

hyperactive behavioral alterations in T2DM mice in the NOR and LD tests. The NOR test was conducted to evaluate explorative activity for novel objects and cognitive function. Interestingly, our T2DM model mice showed an increase in total explorative time without cognitive dysfunction. Sims-Robinson et al. reported that 6-week-old male mice after feeding an HFD for 2 weeks showed increased explorative activity in the NOR test, being in agreement with our results [21]. In the LD test for assessing spontaneous explorative activity and anxiety, our T2DM mice showed an increase in the frequency of transition without a change in the time spent in the light chamber. Kurhe et al. reported that Swiss albino mice fed an HFD for 14 weeks, a duration that is 1.75-times longer than that for our T2DM mice, showed less frequent transition [22], and their results are different from our results. We considered that the length of the feeding period caused the difference in behavioral alterations. Furthermore, the T2DM mice in our study did not show anxiety in the LD test. It has been reported that anxiolytics increased the number of transitions between the light and dark compartments [23] and that an increase in transitions reflects anxiolytic activity [24]. We thought that our model mice showed hyperactive behavioral alterations because they did not have anxiety.

The open abdominal surgery used as surgical stress caused postoperative hypoactivity in the T2DM mice as indicated by the decrease in total distance in the OF test, decrease in explorative activity in the NOR test and decrease in the frequency of transition in the LD test. In the OF test, we evaluated locomotor activity and anxiety behavior. The surgical stress in T2DM mice caused a decrease in total distance moved compared with that before surgery, but there was no difference in the control mice. Zhao et al. reported that 15-month-old male mice fed an HFD for 14 weeks did not show a decrease in total distance in the OF test after internal fixation surgery of a tibial fracture [25]. The discrepancy between our results and their results might have been caused by the differences in type of surgical stress, duration of HFD feeding and age of the mice. Regarding anxiety behavior, the time spent in the center decreased after surgery compared with that before surgery in both the T2DM and control groups. These results indicated that the surgical stress induced anxiety in mice. Our results are supported by the results of a study by Lu et al. showing that 16-month-old Sprague-Dawley rats one day after splenectomy exhibited anxiety-like behavior indicated by traveling less in the central area [26]. Moreover, in the present study, the T2DM mice after surgery showed a decrease of activity in all three behavioral tests. It has been reported that anxiety caused a decrease of transition frequency [27] and a decrease of explorative activity [28]. We considered that the anxiety state induced by surgical stress in the T2DM mice caused the postoperative hypoactivity in the behavioral tests.

Among neurotransmitters, it is well known that an increase of NA release in the brain is an acute response to stress [29] and that NA regulates cognition [30], motivation and social interactions [31]. In the hippocampus, a decrease of NA is associated with mental impairments such as a decrease of activity, depression and cognitive dysfunction [17-19, 32]. In the present study, hippocampal NA level was decreased 24 hours after surgical stress. Regarding the effect of surgery on hippocampal NA, Ying Xu et al. reported that rats with depression caused by olfactory bulbectomy showed a decrease of hippocampal NA two weeks after the surgery [33]. Liu et al. demonstrated that chronic unpredictable mild stress for 6 weeks caused depressive behaviors accompanied by a decrease of hippocampal NA in mice [34].

According to these findings, we considered that the surgical stress in the T2DM model mice induced the decrease of hippocampal NA and that it might be associated with postoperative hypoactivity in the T2DM model mice. This might lead to elucidate the pathophysiology of perioperative mental illness in diabetic patients.

There are some limitations in the current study. First, we conducted the series of behavioral tests in the identical mouse to reduce the total number of mice, and performed within a limited postoperative period. However, some more behavioral experiments including assessments of cognitive function, anxiety and depression-like behavior are should be also conducted to identify the postoperative behavioral changes in more detail. Second, we used open abdominal surgery as surgical stress and examined behaviors 24 hours after the surgery in this study. Further experiments are needed to investigate the effects of different degrees of invasion and time-dependent effects on the behavior and hippocampal NA in the T2DM mice. Finally, we did not observe downstream signaling of hippocampal NA, and it is therefore unclear how the change in hippocampal NA affected perioperative behavioral alterations in this study. Therefore, future research is required to prove it.

Conclusions

In conclusion, we found that T2DM model mice fed an HFD for 8 weeks showed behavioral alterations and that surgical stress in the T2DM model mice caused postoperative hypoactivity and a decrease in hippocampal NA.

Methods

Animals

Four-week-old male C57BL/6J mice, weighted 15.7 (median)±2.7 g, were purchased from SLC Center Japan. We used male mice to avoid the influence of sextual cycle hormone in the behavioral experiments. The animals were group-housed 3 per plastic cage at our animal experimental center until the behavioral tests in a temperature-(24℃), humidity- and light-controlled room (12-hour light-dark cycle) with ad libitum access to water and rodent chow according to the Kobe University standard for animal welfare.

All animal experiments and procedures were performed in accordance with the national institutional guidelines for proper conduct of animal experiments and complied with the international guiding principles for biomedical research involving animals. This study was approved by the Kobe University Animal Experiment Committee (approved on 23th/October/2017, No. P151004).

Experimental protocol

The aim of the current study was to investigate the effect of surgical stress on T2DM model mice. Our experimental protocol is shown in Fig.1. Eighty-four mice were randomly divided into four groups of mice (n = 21 per group, control group, surgery control group, T2DM group, surgery T2DM group). Sample size

was calculated with EZR [35] followed by the results of preliminary behavioral experiment of OF test by using five mice in each T2DM and surgery T2DM group. In each group, fifteen mice were used for the behavioral tests, and six mice were employed to examine the hippocampal NA level. The T2DM groups were fed HFD32 (32% fat content and 56.7% of fat kcal; CLEA Japan, Inc), and the control groups were fed normal rodent chow. Diet intervention was started at 6 weeks of age and lasted for 8 weeks until 14 weeks of age. As biophysical parameters, we investigated body weight every week and fasting blood glucose level every 2 weeks. Glucose tolerance evaluation by an intraperitoneal glucose tolerance test (IPGTT) was performed at 13 weeks of age and hemoglobin A1c (HbA1c) level was examined at 14 weeks of age. At 14 weeks of age, a series of behavioral tests was performed, and surgery was performed for the surgery groups 24 hours before the behavioral tests. After the behavioral tests, mice were euthanized by removing blood transcardially under deep general anesthesia with sevoflurane.

Surgical procedure

Open abdominal surgery was performed in surgical groups (surgery control and surgery T2DM group) according to the previously study [36]. The procedure was conducted at animal raboatory (at 8:00 a.m.). In detail, general anesthesia was induced with 3.5% sevoflurane in 50% oxygen in a plastic chamber and was maintained with 3.5% sevoflurane (covering 1 minimal alveolar concentration (1MAC) of adult C57BL/6J mice [37]) by using mask during the surgical procedure. The concentration of sevoflurane and oxygen in the inhalational anesthesia was continuously monitored by using anesthetic monitoring equipment (Datex, IMI Co., Ltd,). Each mouse was gently restrained to a heating pad (37℃) during the procedure. After shaving the abdominal incision area, sterilization was provided by povidone iodine. A 1-cm vertical incision was made in the middle of the abdomen. During the surgery, the whole small intestine was exteriorized from the peritoneal cavity, covered with moist gauze, and then manipulated with sterile cotton swabs for 1 minute. Afterward, the peritoneum muscle and skin were repaired separately with 5-0 nylon (Natsume Seisakusho Co, Japan). Total anesthesia time was 20 minutes for each procedure. After the closing incision and 8 hours later, EMLA® cream (2.5% lidocaine and 2.5% prilocaine) was applied to treat the surgery-associated pain [38].

Body weight and fasting blood glucose level

After food intervention, body weight was recorded every week and blood glucose level was examined every 2 weeks. The fasting glucose level was measured by Glutest Neo α (Sanwa Kagaku Kenkyusho, Japan) following 6 hours of fasting [39].

Intraperitoneal glucose tolerance test (IPGTT)

At 13 weeks of age, 7 weeks after food intervention, IPGTTs were performed. The animals were fasted for 16 hours prior to the glucose tolerance test. After measuring basal levels of blood glucose (0 minutes), each animal was injected with glucose solution (2 g glucose/kg body weight) intraperitoneally (i.p.), and blood glucose was measured at 15, 30, 60 and 120 minutes after the injection [39].

Hemoglobin A1c (HbA1c)

At 14 weeks of age, blood samples were collected from the tail vein and HbA1c was measured by using a glycated hemoglobin A1c kit (DCA 2000® HbA1c cartridge, Simens Healthineers Japan).

Behavioral tests

We performed a series of sequential behavioral tests to evaluate perioperative behaviors. For the surgical groups, behavioral tests were performed 24 hours after the open abdominal surgery. Every mouse was isolated in an individual cage and transferred to the test room for habituation one hour before the behavioral tests. The orders of mice for the test were in a random manner and the test chamber was cleaned after each session. Every behavioral test was automatically recorded. The behavioral tests were performed at 8:00 AM to 15:00 PM in the light phase. The details of the series of behavioral experiments are as follows.

Open field test (OF test)

An open field test was used for measuring locomotor activity and anxiety [40]. The open field apparatus was constructed of a gray acrylic plate of 60 × 60 cm in size with 40 cm walls. Each mouse was placed close to the wall of the apparatus and exposed to the novel environment, and activity was monitored for 5 minutes twice with a one-hour interval. Activity was automatically recorded by a video tracking system [41] and analyzed by using the SMART® system (Bio Research Center Corporation, Japan). Repeated exposure to the open field apparatus results in acclimation to the field for the novel objective recognition test [42].

Novel objective recognition test (NOR test)

The NOR test was performed to evaluate both explorative activity for objects and cognitive ability. One hour after the open field test, the NOR test was performed in the same apparatus. The test consists of two phases; a familiarization phase and a testing phase. In the familiarization phase, two identical objects, glass beakers (5.5 cm in diameter × 7 cm in height), were placed 20 cm from each side wall of the chamber and 20 cm apart. The familiarization phase was performed for 5 minutes and each animal was returned to its home cage after the familiarization phase. In the testing phase one hour after the familiarization phase, one of the familiar objects was replaced with a novel object, a plastic ball (7 cm in diameter). The testing phase was performed for 5 minutes. The time spent exploring each object was recorded and analyzed by the SMART® system. Cognitive outcome was determined by the “discrimination index”. The discrimination index (%) was calculated as the time spent in the novel object zone × 100 / (time spent in old object zone + time spent in novel object zone) [43].

Light-dark box test (LD test)

The LD test was performed one hour after the NOR test to investigate spontaneous explorative activity and anxiety behavior. The new environment and light are known as mild stressors and an innate aversion

response to the light chamber represents explorative and anxiety behavior of rodents [44]. The LD test apparatus consists of bright and dark compartments (length of 18 cm × width of 30 cm × height of 16 cm) connected by a small opening (10 cm in diameter, semicircle shape). To evaluate the naive behavior of mice in the usual state without excessive stress, the light chamber was illuminated (200 lux), whereas the dark chamber was 1-2 lux. The LD test was performed for 5 minutes. The total number of transitions and the time spent in the light chamber were recorded on video.

High-performance liquid chromatography (HPLC)

Hippocampal NA concentration was measured by HPLC. Hippocampal tissues of six mice in each group for evaluating NA were collected after beheading the mice and were homogenized in 0.4M perchloric acid in a ratio of one part tissue to ten parts perchloric acid and centrifuged at 4,000 g for 20 minutes at 4℃. Then the supernatant was collected and preserved at -80℃ until sample analysis. Samples were purified by using MonoSpin® (GL Sciences Inc. Japan). NA level was measured by the HPLC system and 3,4-dihidroxybenxoylamin was used as the internal standard. Respective peak and elution times of the samples were evaluated by relative comparison to standard. Chromatographic separation was performed on an Inertsil ODS-4 column, 5 µm, 250 × 3.0 mm I.D. (GL Sciences Inc, Japan). The column temperature was maintained at 35 ℃. The flow rate was 0.5 mL/min. Injection volume was 20 µL. The mobile phase consisted of acetate-citrate buffer and acetonitrile. The mobile phase was composed of 20 mM citric acid, 20 mM citric acid monohydrate, 4.6 mM 1-octanesulfonic acid sodium and 13.7% acetonitrile. The electrochemical detector ED703, Diamond was used to detect monoamine.

Statistical analysis

Statistical analysis by comparison between two groups (control vs T2DM, surgery control vs surgery T2DM, control vs surgery control and T2DM vs surgery T2DM) was conducted using EZR [35] and JMP Statistical Discovery™ (SAS Institute Inc, Japan). The data for the behavioral test, and for hippocampal NA and HbA1c levels were analyzed by the Mann-Whitney U test using EZR. Body weight, fasting blood glucose level and IPGTT were subjected to two-way repeated measures analysis of variance (ANOVA) by using JMP. P values less than 0.05 were considered significant difference. In the figure, error bar of data is presented as medians ± quartile for the Mann-Whitney U test and means ± SD for ANOVA.

List Of Abbreviations

ANOVA: Analysis of variance; HbA1c: hemoglobin A1c; HFD: high fat diet; HPLC: high-performance liquid chromatography; IPGTT: intraperitoneal glucose tolerance test; NA: noradrenaline; NOR: novel objective recognition; LD: light-dark; OF: open field; T2DM: type 2 diabetes mellitus

Declarations

Ethics approval and consent to participate

All animal experiments and procedures were performed in accordance with the national institutional guidelines for proper conduct of animal experiments and complied with the international guiding principles for biomedical research involving animals. This study was approved by the Kobe University Animal Experiment Committee (approved on 23th/October/2017, No. P151004).

Consent for publication

Not applicable.

Availability of data and materials

The raw datasets supporting the results of this study are available in the Mendeley Data, v1. doi.org/10.17632/dphnhn3kjw.1. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interest

The authors declare that they have no competing interests.

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Authors' contribution

MN performed the experiment, completed data analysis and drafted the manuscript. YN and SM were major contributor in writing the manuscript. YN, ME and NO help to design the study. MT supported to perform the experiments of HPLC. All authors read and approved the final manuscript.

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Figures

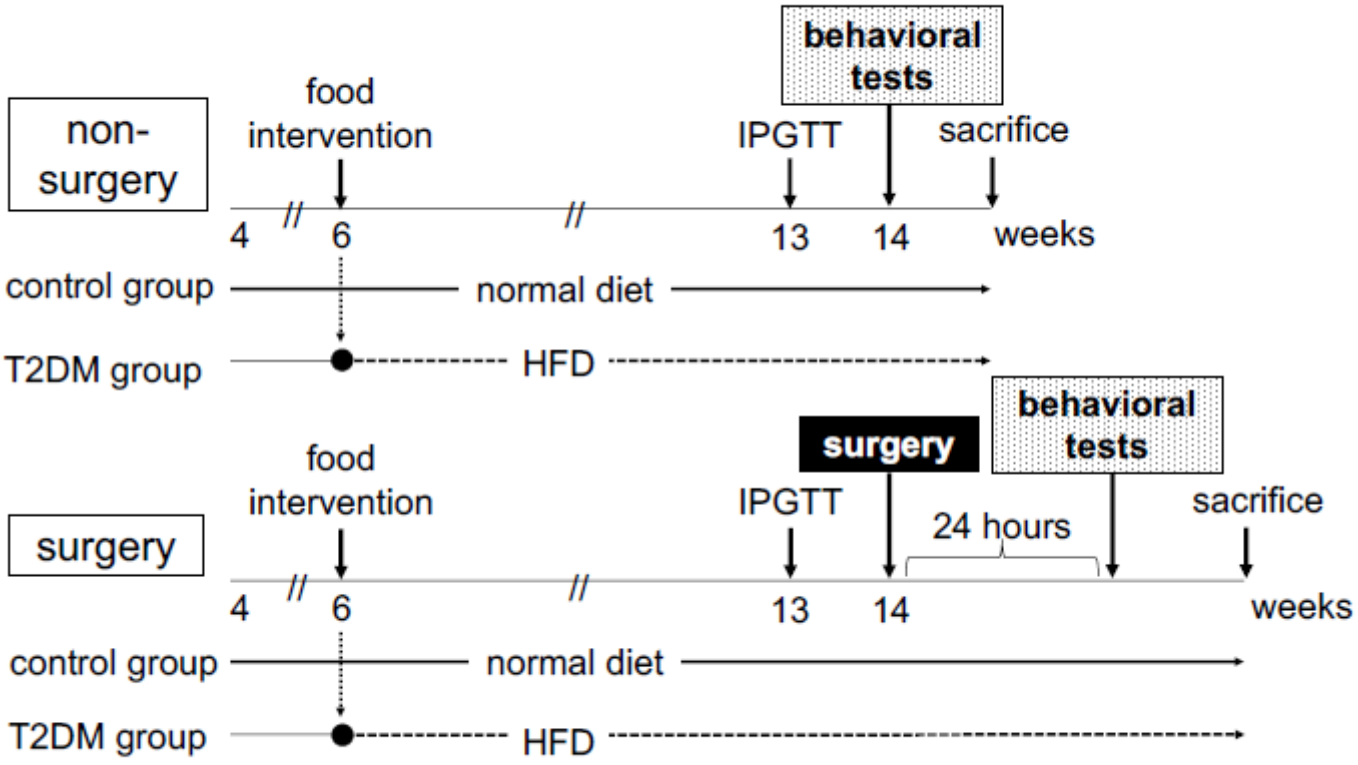

Figure 1

Experimental procedure in this study. T2DM: type 2 diabetes mellitus, HFD: high fat diet, IPGTT: intraperitoneal glucose tolerance test.

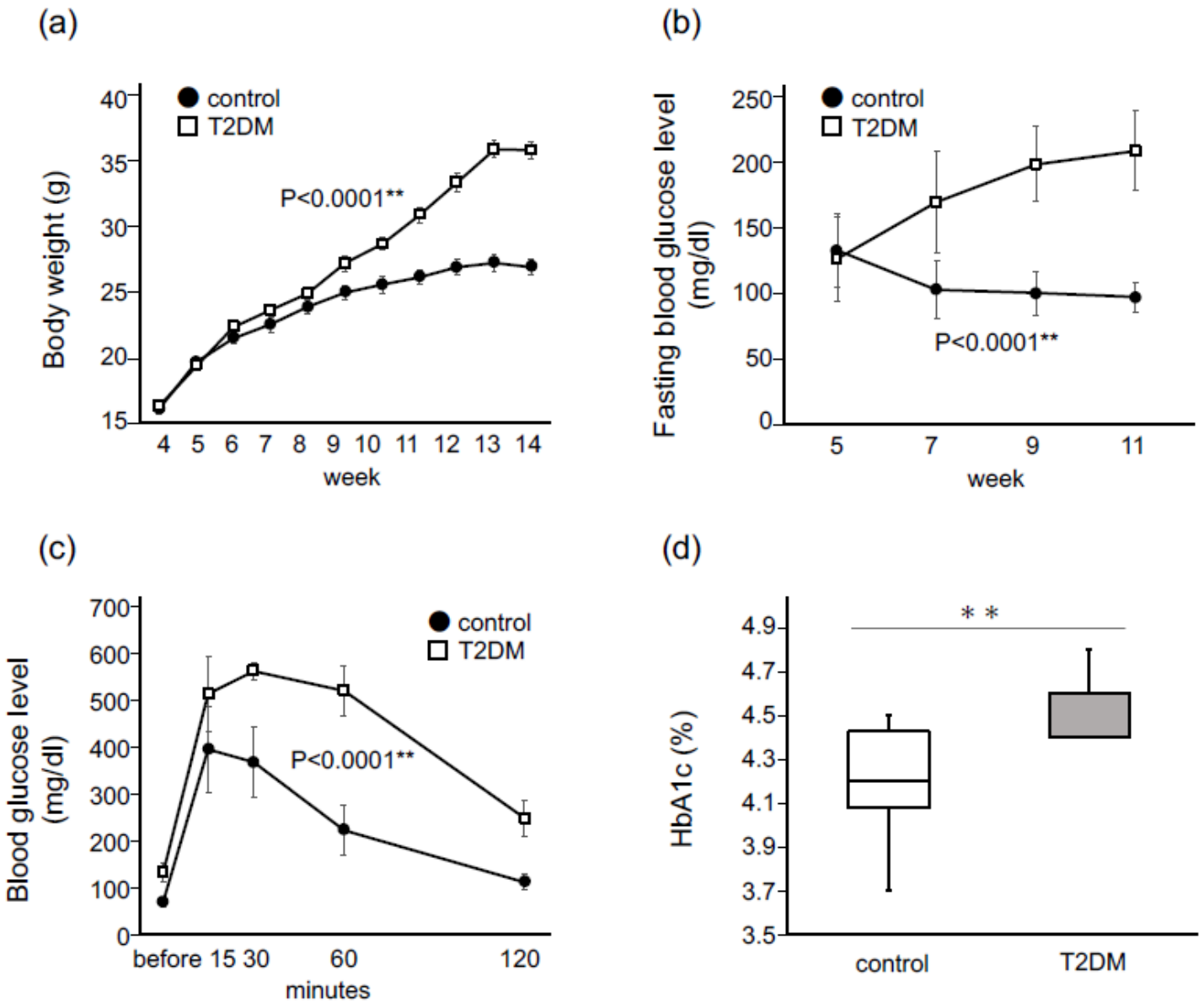

Figure 2

Biophysical parameters in the T2DM model mice. (a) Comparison of body weight gains in the control and T2DM groups. The body weight gain of T2DM mice was significantly greater than that of control mice. (b) The fasting blood glucose level in the T2DM group was significantly higher than that in the control group. (c) In the IPGTT, the glucose level in the T2DM group was significantly higher than that in the control group, and prolonged hyperglycemia was observed in the T2DM group. (a-c) The line with circles indicates the control group and the line with squares indicates the T2DM group. The results are shown as means ± standard deviation, n = 12 per group. (d) The HbA1c level in the T2DM group was higher than that in the control group. The white bar indicates the control group and the gray bar indicates the T2DM group. The results are shown as medians ± quartile, n = 15 per group. **; P<0.01

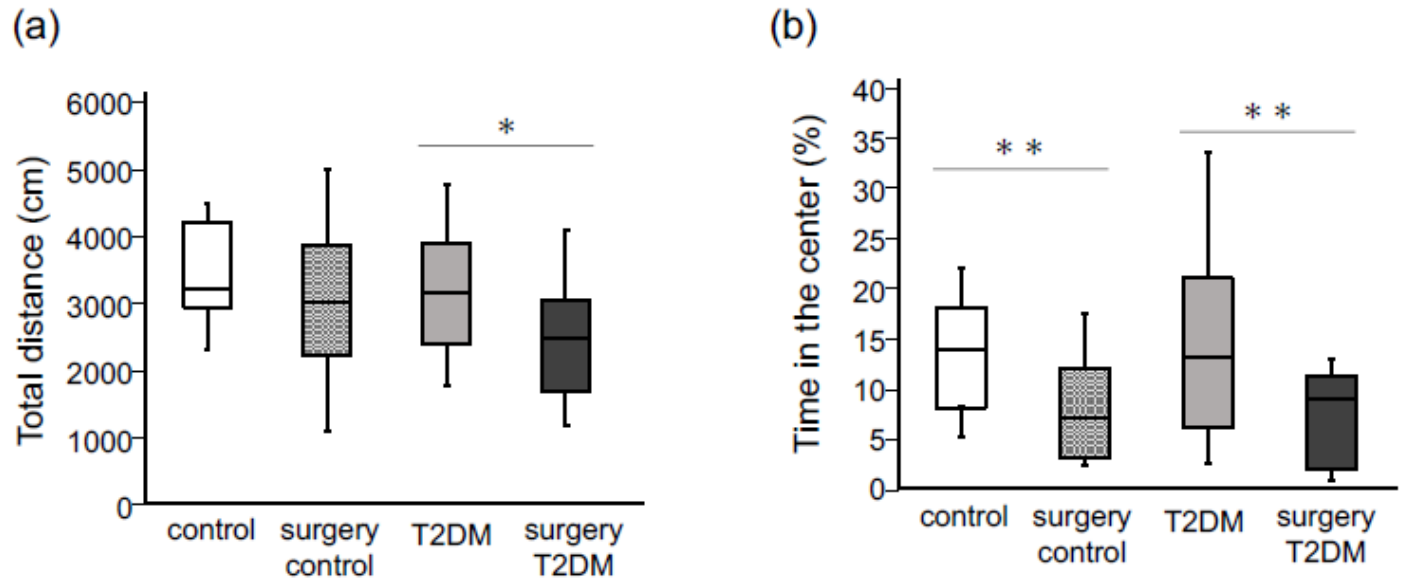

Figure 3

The results of the open field (OF) test. (a) Total distance in the OF test. The total distance was significantly shorter in the surgery T2DM group than in the T2DM group. (b) Time spent in the center area in the OF test. The time spent in the center was significantly decreased after surgery in both the control group and T2DM group. Each graph is shown as medians ± quartile, n = 15 per group. *; P<0.05, **; P<0.01.

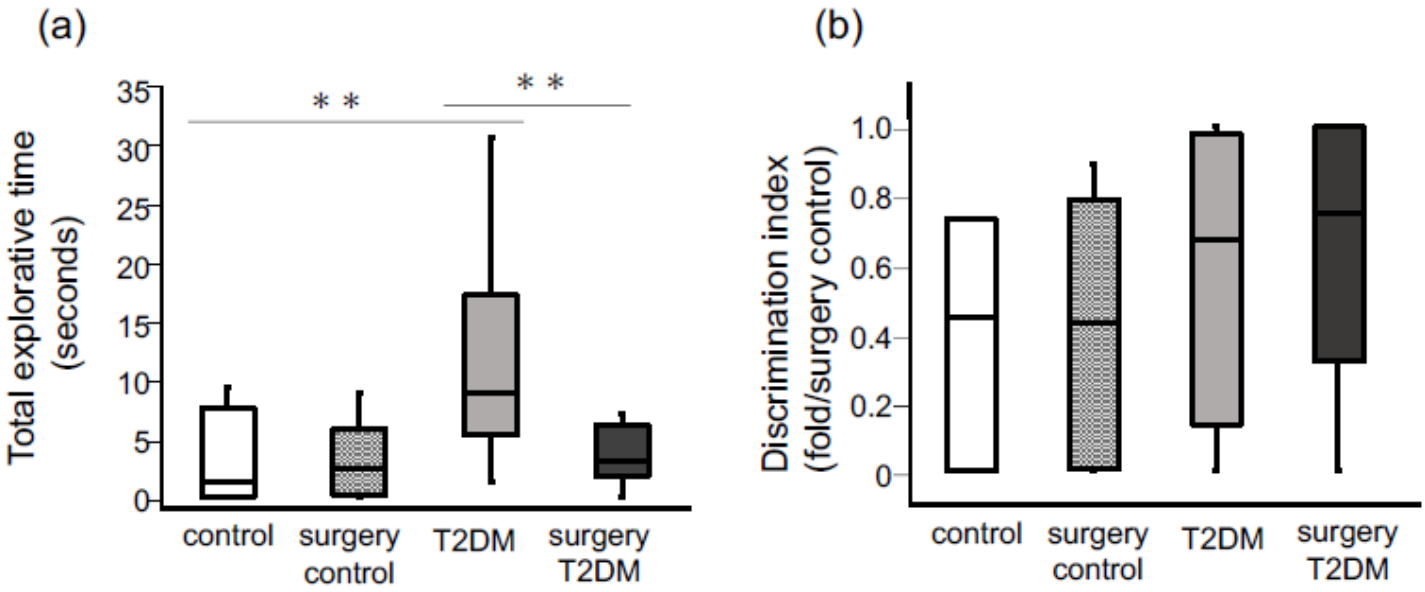

Figure 4

The results of the novel objective recognition (NOR) test. (a) Total explorative time in the NOR test during the familiarization phase. The total explorative time was significantly longer in the T2DM group than in the control group. However, the explorative activity was significantly decreased after surgery in T2DM mice. (b) Discrimination index in the NOR test. There was no difference between the control group and T2DM group during the perioperative period. Each graph is shown as medians ± quartile, n = 15 per group. **; P<0.01.

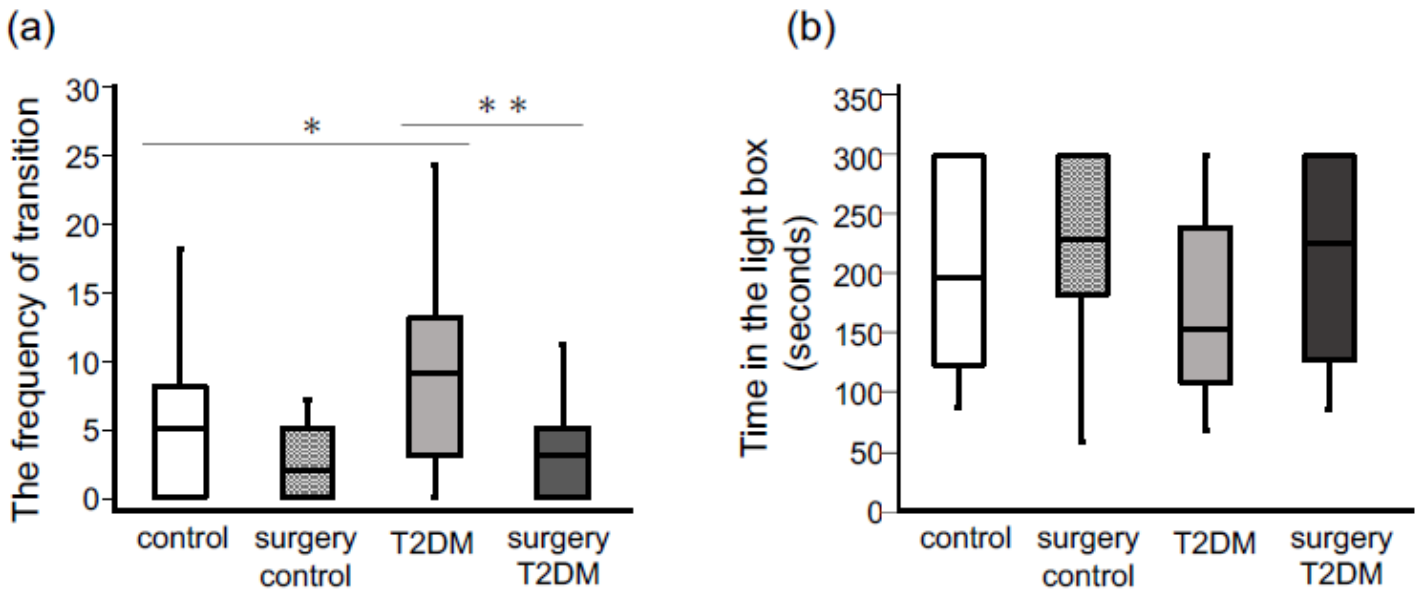

Figure 5

The results of the light-dark (LD) test. (a) Frequency of transition in the LD test. The number of transitions in the T2DM group was significantly larger than that in the control group. However, the number of transitions significantly decreased after surgery in the T2DM mice. (b) Time spent in the light box. There was no difference between the control group and the T2DM group during the perioperative period. Each graph is shown as medians ± quartile, n = 15 per group. *; P<0.05, **; P<0.01.

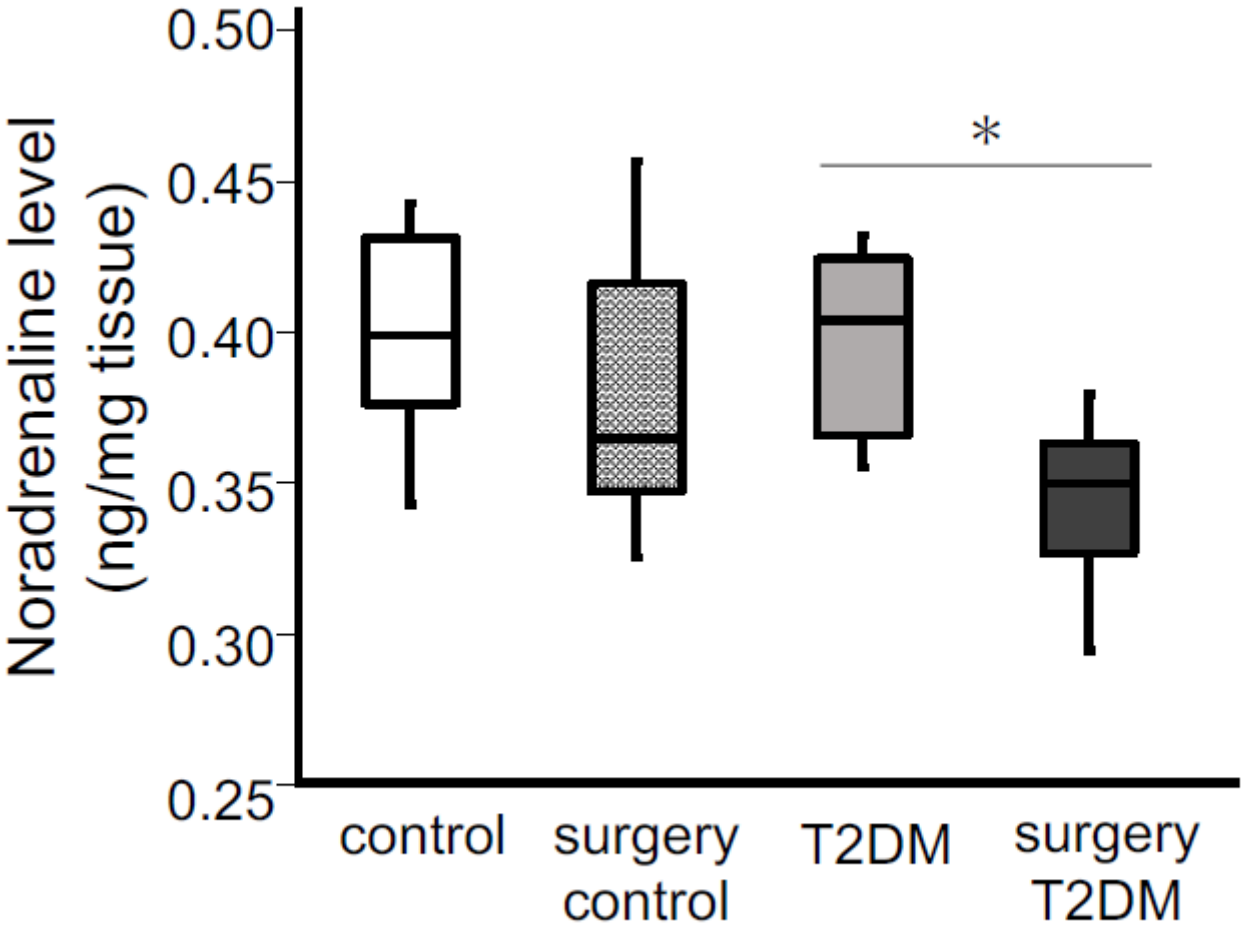

Figure 6

Noradrenaline concentration in the hippocampus determined by high-performance liquid chromatography. The hippocampal noradrenaline concentration was significantly decreased after surgery in T2DM mice. Each bar is shown as median ± quartile, n = 6 per group. *; P<0.05.

Supplementary Files

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