

Fructose Consumption Decreases Bodyweight Gain, Reduces Anxiety, Modulates Spatial Memory and Increases Dopamine but Not Serotonin Metabolism

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Abstract

Objectives: A global rise of obesity is thought to be due to greater consumption of fructose rich processed food. This study is designed to investigate whether long term consumption of fructose alone, not added to food, can produce greater weight gain in rats to lead to obesity. Some behavioral and neurochemical effects of long-term fructose consumption are also determined.

Methods: Animals were treated orally with fructose (4 g/day) for 6 weeks. Food and calorie intake and body weight change, anxiety-like effects in elevated plus maze (EPM) and activity in open field (OF) were monitored weekly. Effects on learning and memory were monitored using Morris water maze (MWM) test after 5 weeks of treatment. Serotonin (5-hydroxytryptamine; 5-HT), dopamine (DA) and their metabolites were determined using HPLC-ECD.

Results: Fructose treatment decreased food intake and body weight and produced no effect on calorie intake. It resulted in the enhancement of exploratory activity in an OF and reduction of anxiety in EPM test. It improved learning acquisition as well as memory retention but impaired reference memory. The levels of 5-HT were reduced in the hippocampus and not altered in the hypothalamus. DA metabolism increased in the hippocampus as well as the hypothalamus.

Discussion: Long term consumption of fructose reduces weight gain, reduces anxiety and produces mixed effects on learning and memory. Serotonin has little role in these effects of fructose but an increase in DA neurotransmission via the hippocampus and hypothalamus may lead to these behavioral changes. Palatability of fructose added food products but not the fructose alone can contribute to global rise in weight gain and obesity.

Keywords: Fructose; Anxiety; Learning; Memory; Motor Activity; Serotonin; Hippocampus; Hypothalamus

Abbreviations

ASP: Approved Animal Study Protocol; DOPAC: 3, 4-Dihydroxy-Phenylacetic Acid; DA: Dopamine; EPM: Elevated Plus Maze; EDTA: Ethylenediaminetetraacetic Acid; g: Gram; HPLC-ECD: High-Performance Liquid Chromatography with Electrochemical Detector; HVA: Homovanillic Acid; hs: Hours; 5-HIAA: 5-Hydroxyindoleacetic Acid; 5-HT: 5-Hydroxytryptamine; kcal: Kilo Calorie; min: Minute; MWM: Morris Water Maze; NIH: National Institute of Health; OF: Open Field; RMD: Repeated Measure Design; s: Seconds; SD: Standard Deviation; SPSS: Statistical Package for Social Sciences.

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Introduction

Exposure to palatable foods that leads to food reward is known to have an important role in overeating leading to obesity. Sweetness usually makes food palatable and these foods are highly consumed [1]. Fructose is widely used as sweetener in food industry in the form of high-fructose corn syrup [2]. Since, fructose has been promoted as a hunger depressant [3], as a diet for insulin independent diabetics [4,5], for parenteral feeding, and as a nutrition supplement to strength athletes [6], its use is considerably increasing. As a moiety of the sucrose molecule, fructose has been accepted as being primarily accountable for the metabolic effects of high-sucrose diets [6-8].

The metabolic fate of fructose is different from glucose [9,10], therefore it doesn't stimulate insulin secretion or leptin production [8] that suggest increased energy intake and body weight gain by dietary intake of fructose [1,2,11]. Many studies have suggested that the boosted use of fructose-rich syrups and other carbohydrates have resulted in the present epidemic of obesity and type-2-diabetes mellitus [2,12,13]. Accumulating evidence shows an association between obesity and mental illnesses such as depression/anxiety and impaired in cognitive functions [14]. Considering the relationship between obesity and mental illnesses, it is important to note that obesity may be either a cause or a consequence of mental distress. Moreover, not only metabolic dysregulation that occur in obesity can affect neuronal function to lead to excessive anxiety and cognitive decline, but obesity and overweight related psychological distress and body shape dissatisfaction can be a risk factor for mental illnesses. To rule out the possibility of psychological distress in the pathophysiology of obesity and to understand the potential mechanism involved in the association of obesity with reported mental illnesses, studies on experimental animals have gained attention.

The present study concerned effects of long-term consumption of fructose on body weight changes, food, and calorie intake and anxiety like behavior and learning and memory. Associated changes in the metabolism of serotonin (5-hydroxytryptamine, 5-HT), dopamine (DA) the neurotransmitters involved in anxiety, learning/memory and food intake [15-17] were also determined in the hippocampus and hypothalamus.

Materials and Methods

Animals

Male albino Wistar rats, weighing 180 - 220 grams was taken from the institutional Animal Research Facility. Rats were caged individually, 7 days before beginning of the actual experiment, under standard temperature ($22 \pm 2^\circ\text{C}$) with 12-hour light and dark cycle, for familiarization with the environment. They were supplied standard rodent diet in cubes form and tap water *ad libitum* till the end of the experiment. All behavioural activities were carried out during the light phase between 10:00 AM to 12:30 PM. The study was designed and conducted in accordance with the National Institute of Health (NIH) guidelines for the Care and Use of Laboratory Animals and an approved animal study protocol (ASP No: 2016-0030) by an Institutional Committee for Animal Care and Use. To avoid time and other effects all experiments were carried out in an equitable design.

Experimental protocol

16-rats were randomly divided into control (water) and fructose treated group so that each of the group had eight animals. Given amount (4 g/day) of fructose was dissolved in water and administered orally. Change in body weight, food and calorie intake was measured between 09:00 am to 9:30 am weekly. Activity in an OF and EPM was monitored on the 7th and 8th day and then at weekly till the end of the experiment, 2- hours (hs) after the fructose administration between 11:00 am to 01:00 pm. On the 39th day of the experiment animals were trained in MWM by giving three successive trails between 10:00 am to 01:00 pm. Learning acquisition was assessed on the same day after 3-hs of training. Memory retention was monitored next day, after 24-hs of training between 10:00 am to 11:00 am. Two days after the training reference memory was evaluated between 10:00 am to 11:00 am. Animals were sacrificed between 11:00 am to 12:00 pm and selected brain regions and serum was collected. Immediately samples were transferred and stored at -80°C until biochemical analysis.

Behavioral studies

Monitoring food and calorie intake and body weights changes

After the end of acclimation period, each animal was given a pre-weighed food in built-in hopper of the cage. Body weight and food intake (g) was measured using digital balance (Sartorius) by placing the animal or food on the pan of the balance between 09:00 am and 10:00 am at the start of the experiment and then on weekly and reported as weekly body weight and food intake [18-20]. Caloric intake (kcal) was calculated by multiplying total food consumed during the week to its caloric value per gram. Increase in body weight was calculated as described before by Haleem [21].

Open field test

This test is used to assess activity of the target animal in the novel environment. This approach is essentially same as described previously [19,22,23]. The apparatus was consisted of a squared box of 76 cm square area with 42 cm high opaque border walls. The floor was divided into 25 equal squares of 15 cm size by black lines. To monitor the activity of the rat, it was placed in the most central square of the box, shortly after that the number of squares crossed by rat with all four paws were counted for a time period of 5 minutes. The apparatus was cleaned after removal of each rat. Control and each fructose treated rats were tested in a balance design to avoid the order effect.

Elevated plus maze test

This model is used to evaluate the anxiety like behavior of target animal, as described previously [19,23]. This device was made up of white acrylic plastic with 50 cm long and 10 cm wide four arms, organized in the shape of plus sign, elevated 60 cm from the ground. Two arms of the maze had no side or end walls called as “open arms”, while the other two arms “the closed arms”, had 15 cm high side and end walls, but the top was open. A central 10 cm square region of the maze at the junction of open and closed arms gave access to all arms. Activity in the maze was monitored by placing a rat in the central square region between closed and open arms. The rat was given free access to explore both arms for a period of 5-minutes. The number of entries and time spent in the open arm during the exposure was carefully observed. The apparatus was cleaned after the completion of each animal. Control and fructose treated animals were tested in a balanced design to avoid the order effect.

Morris water maze test

This model is used to assess the short term, long term and reference memory of the rat as stated previously by Cheema Nawaz., *et al.* [23], Haleem Nawaz., *et al.* [20], Salman Nawaz., *et al.* [24]. The apparatus was composed of a white circular pool made up of plastic. The diameter and height of the apparatus was 90 cm and 37 cm respectively. The maze was equipped with a rigid platform of 10 cm square top and 28 cm height at one pole. The apparatus was filled with water ($24 \pm 2^\circ\text{C}$) up to the depth of 30 cm and made opaque by addition of adequate quantity of pure milk. Escape from the water was given by means of a camouflaged platform which was typically dipped 2 cm beneath the water surface in a fixed position (North Pole). The pool was divided into four equivalent quadrants as: North (N), South (S), East (E), and West (W).

The first phase of the experiment was started from the training of the each animal between 10:00 am to 01:00 pm. During the training session, each animal was given chance of three trials starting from three different poles with respect to the North Pole containing the platform. The time span between each trial was 60 seconds (s). During first trail, each animal was placed at the South Pole for a maximum time length of 120s to find the hidden platform and to stand on it. The animal who found the platform within given time period was allowed to stay on the platform for 10s, however, the animal who failed to find the platform within the stipulated time were gently guided to the platform. This procedure was repeated for each trail of the training.

During the memory evaluation phase, which consisted of learning acquisition and memory retention, each animal was placed at the South Pole and it's time to reach and mount on the platform for a maximum time length of 60s was recorded. The learning acquisition was performed after 3-hs of the training between 01:30 pm - 04:30 pm while memory retention was performed 24-hs after the training between 10:00 am - 11:00 am.

Reference memory

Following the short and long term memory assessment, reference memory was evaluated in the probe test in which platform, which was previously placed at the North Pole, was removed from the water maze. Reference memory was monitored on the next day of memory retention between 10:00 am - 11:00 am. All the physico-environmental conditions of the experiment were same as mentioned earlier. Animals were introduced from the South Pole of the apparatus which was just opposite to the pole where platform was placed previously. They were allowed to swim freely for 60s just after the stipulated time of fructose administration in an ordered way. Latency time (s) to reach the reference Pole or quadrant (quadrant having platform previously), number of entries and total time spent at reference quadrant was recorded. Reduced latency time, increased number of entries and greater time spent at reference quadrant was considered as the measure of memory consolidation.

Determination of serotonin, dopamine, and their metabolites

Frozen brain sample were homogenized in extraction medium, composed of sodium metabisulfite (0.1%), cysteine (0.01%), EDTA (0.01%), perchloric acid (0.4M). The homogenate was centrifuged at 6000 rpm for 15 minutes (min). The supernatant was collected and processed for further analysis by HPLC-ECD as reported previously [19,20]. 5-HT, DA and their metabolites were estimated using an electrochemical detector (Waters®, e2465 ECD) via an alliance separation module (Waters®, e2695). Sample aliquots (20 µL) were injected at the top of the column (Waters® Spherisorb®S5 5 um ODS2 4.6 × 150 mm) by an auto-sampler. Mobile phase was consisted of sodium phosphate buffer (0.1M) having methanol (10%), sodium dihydrogen phosphate dehydrate (1.56%), sodium octyl sulfate (0.023%) and EDTA (0.005%) at pH 2.9. Separation was accomplished at an operating potential of + 0.8 - 1.0 volt and a pressure of 1000-2000 psi.

Statistical analysis

Data are presented as means ± SD. Data on food and calorie intake, body weight, growth rate and behaviour in EPM and OF and MWM were analyzed by two-way ANOVA repeated measure design (RMD). Post hoc comparisons were done using Tukey's test. Reference memory and neurochemical data were analyzed by t-test. SPSS Software version 21.0 was used for statistical analysis. P values < 0.05 were consider significant.

Results

Effects on Food and Water Intake and Growth Rate

Figure 1 shows the effect of fructose on weekly food and calorie intake and body weight change. Analysis of data on food intake (1A) by two-way ANOVA repeated measure design (RMD) revealed significant repeated measure (weeks) ($F = 50.336$, $df 6, 84$ $p < 0.05$) and treatment ($F = 16.531$, $df 1, 14$ $p < 0.05$) effect. Interaction between weeks and treatment ($F = 1.830$, $df 6, 84$ $p > 0.05$) was not significant. Similarly, data on caloric intake (1B) analyzed by two-way ANOVA (RMD) revealed significant effect of repeated measure (weeks) ($F = 50.596.22$, $df 6, 84$ $p < 0.05$) and treatment ($F = 5.583$, $df 1, 14$ $p < 0.05$), however interaction between weeks and treatment ($F = 1.703$, $df 6, 84$ $p > 0.05$) was not significant. Data on body weight (1C) showed significant effect of repeated measure (weeks) ($F = 100.690$, $df 6, 84$ $p < 0.05$). The effect of treatment ($F = 2.995$, $df 1, 14$ $p > 0.05$), was not significant. Interaction between weeks and treatment ($F = 2.145$, $df 6, 84$ $p > 0.05$) was also not significant. Data on body weight increase (1D) also showed significant effect of repeated measure (weeks) ($F = 67.82$, $df 5, 70$ $p < 0.05$) and treatment ($F = 12.90$, $df 1, 14$ $p < 0.05$). Interaction between weeks and treatment ($F = 1.32$, $df 5, 70$ $p > 0.05$) was not significant.

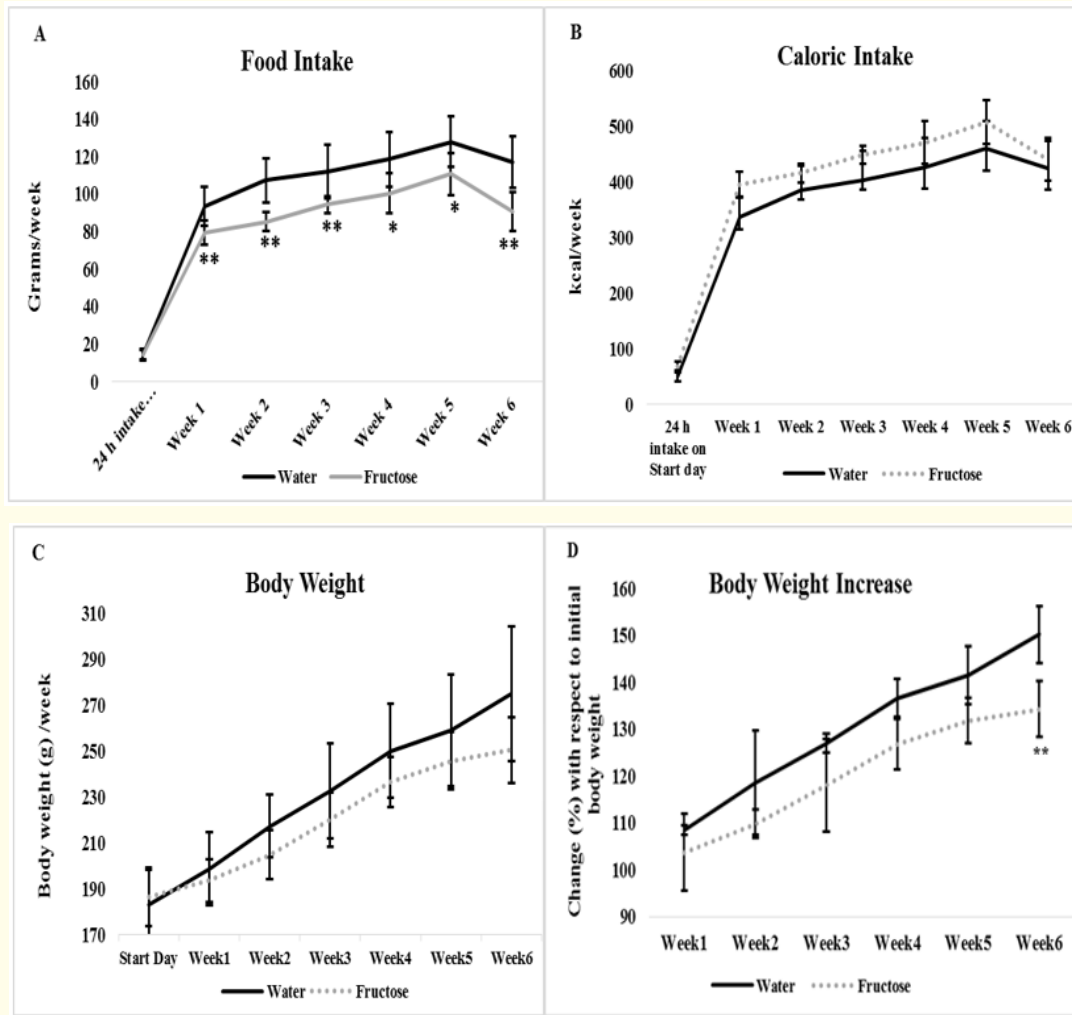


Figure 1: Effects of 6-weeks fructose intake (4 g/day) on food (A) calorie (B), body weight change (C and D). Values are means \pm S.D (n = 8). Significant difference by Tukey's test: *p < 0.05, **p < 0.01 from respective water-treated rats following two-way ANOVA (RMD).

Post hoc comparison by Tukey's test showed that 6-weeks treatment of animals with fructose decreased food intake (weekly) and body weight gain. Post hoc comparison by Tukey's test also showed that increase in calorie intake in fructose treated rats were not significant.

Effect on OF activity

Figure 2 shows exploratory activity of animals treated with fructose in an OF test. Analysis of data by two-way ANOVA (RMD) revealed significant repeated measure (weeks) ($F = 3.52, df 4, 56, p < 0.01$) and treatment ($F = 34.03, df 1, 14, p < 0.01$) effect. Interaction between weeks and treatment ($F = 1.63, df 4, 56, p > 0.05$) was not significant. Post hoc comparison by Tukey's test revealed that administration of fructose increased exploratory activity in the OF after week1-week5.

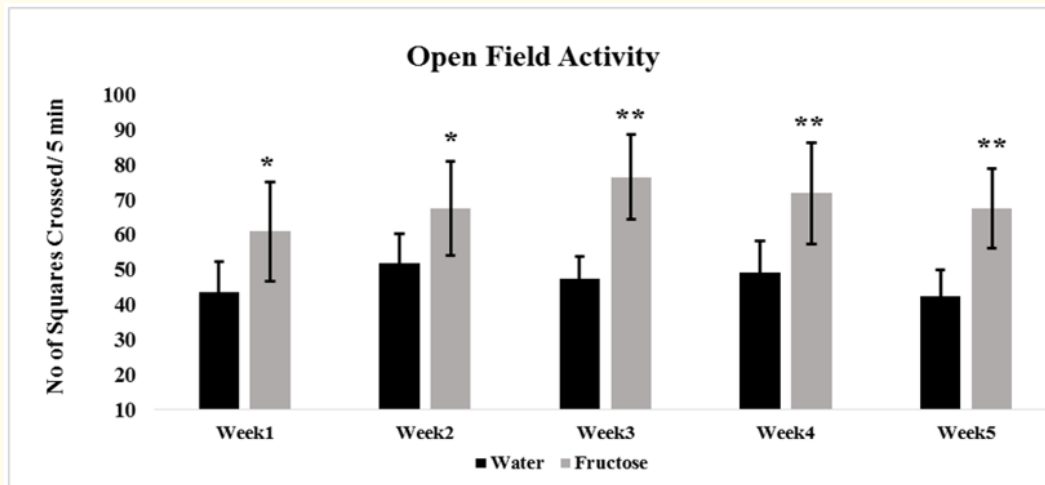


Figure 2: Effects of 5-weeks (4 g/day) administration of fructose on exploratory activity in OF test. Values are means \pm S.D (n = 8). Significant difference by Tukey’s test: *p < 0.05, **p < 0.01 from respective water-treated rats following two-way ANOVA (RMD).

Effect on EPM activity

Figure 3 shows performance of animals treated with the fructose in the EPM test. Analysis of data on entries in the open arm of EPM (3A) by two-way ANOVA (RMD) showed significant effect of repeated measure (weeks) (F = 21.88, df 4, 56 p < 0.05) and treatment (F = 662.06, df 1, 14 p < 0.05). Interaction between weeks and treatment was also significant (F = 19.53, df 4, 56 p < 0.05). Post hoc comparison by Tukey’s test showed that fructose treated animals exhibited a greater number of entries in the open arm.

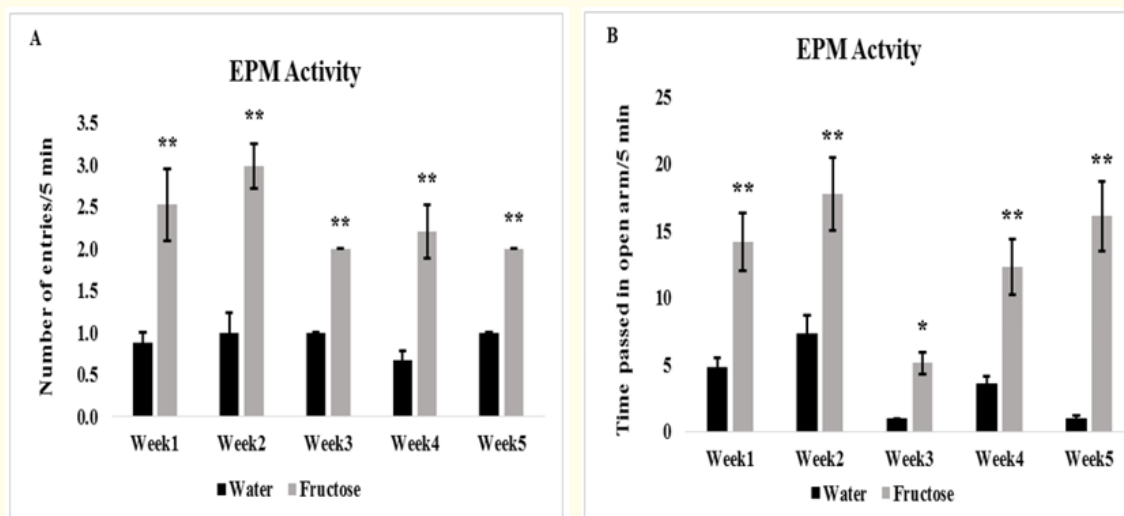


Figure 3: Effects of 5-weeks (4 g/day) administration of fructose on EPM test (3A, B). Values are means \pm S.D (n = 8). Significant difference by Tukey’s test: *p < 0.05, **p < 0.01 from respective water-treated rats following two-way ANOVA (RMD).

Analysis of data on time passed (s) in open arm of EPM test in (3B) by two-way ANOVA (RMD) also showed significant effect of repeated measure (weeks) ($F = 64.76$, $df = 4, 56$ $p < 0.05$) and treatment ($F = 1053.59$, $df = 1, 14$ $p < 0.05$). Interaction between weeks and treatment ($F = 21.27$, $df = 4, 56$ $p < 0.05$) was also significant. Post hoc comparison by Tukey's test revealed that fructose treated animals exhibited a greater time span in the open arm after week1-week5 showing anxiolytic-like effect of fructose.

Effects on MWM test

Figure 4 shows performance of animals treated with the fructose in the MWM test. Analysis of data on learning acquisition and memory retention (4A) by two-way ANOVA (RMD) showed significant days ($F = 66.861$; $df = 1, 14$ $p < 0.05$) and treatment ($F = 169.463$; $df = 1, 14$ $p < 0.05$) effect. The interaction between days and treatment ($F = 51.635$; $df = 1, 14$ $p < 0.05$) was also significant. Post hoc comparison showed that learning acquisition as well as memory retention (A) was improved in fructose treated animals.

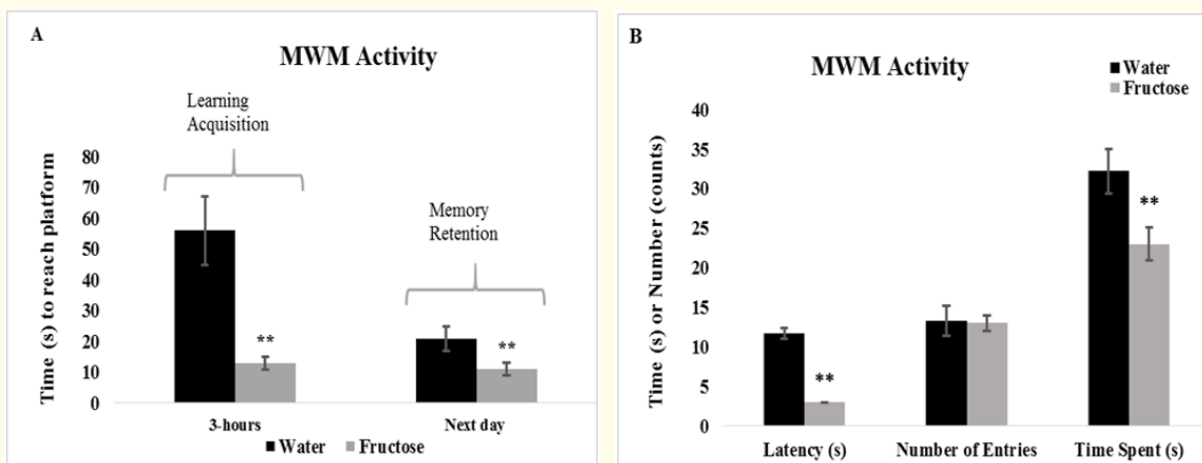


Figure 4: Effects of 5-weeks (4 g/day) administration of fructose on spatial learning and memory in MWM test.

Values are means \pm S.D ($n = 8$) in the presence (A) and absence (B) of submerged platform. Significant difference in (A) by Tukey's test: $*p < 0.05$, $**p < 0.01$ from water-treated rats following two-way ANOVA (RMD). Significant difference in (B) by independent sample t -test: $**p < 0.01$ from water-treated rats.

Analysis of data on reference memory (4B) by independent sample t -test revealed that fructose treatment decreased the latency time (s) to reach the reference quadrant, where previously platform was placed ($F = 75.493$; $df = 3, 20$ $p < 0.05$) and the time spent (s) ($F = 2.465$; $df = 1, 14$ $p < 0.05$). T -test also showed that the number of entries ($F = 11.667$; $df = 1, 14$ $p > 0.05$) in the fructose treated animals were not changed.

Effects on hippocampal and hypothalamic DA and 5-HT and their metabolites

Figure 5 and 6 show the levels of DA and 5-HT in the hippocampus of the fructose-treated rats. Analysis of the data by independent sample t -test showed decreased DA levels (5A) ($F (1, 14) = 2.963$; $p < 0.05$), and increased DOPAC (5B) ($F (1, 14) = 1.127$; $p < 0.05$) and HVA levels (5C) ($F (1, 14) = 4.754$; $p < 0.05$) in the hippocampus. Similarly, the levels of 5-HT (6A) ($F (1, 14) = 5.021$; $p < 0.05$) were also decreased, but the levels of 5-HIAA (6B) ($F (1, 14) = 1.170$; $p > 0.05$) were not changed in the hippocampus. Figure 7 and 8 show the levels of DA and 5-HT in the hypothalamus of fructose-treated rats. Analysis of the data by independent sample t -test showed a significant increase in the levels of DA (7A) ($F (1, 14) = 9.419$; $p < 0.05$), DOPAC (7B) ($F (1, 14) = 0.290$; $p < 0.05$) and HVA (7C) ($F (1, 14) = 13.4$; $p < 0.01$), while no changes in the levels of 5-HT (8A) ($F (1, 14) = 1.047$; $p > 0.05$) and 5-HIAA (8B) ($F (1, 14) = 1.168$; $p > 0.05$) in the hypothalamus.

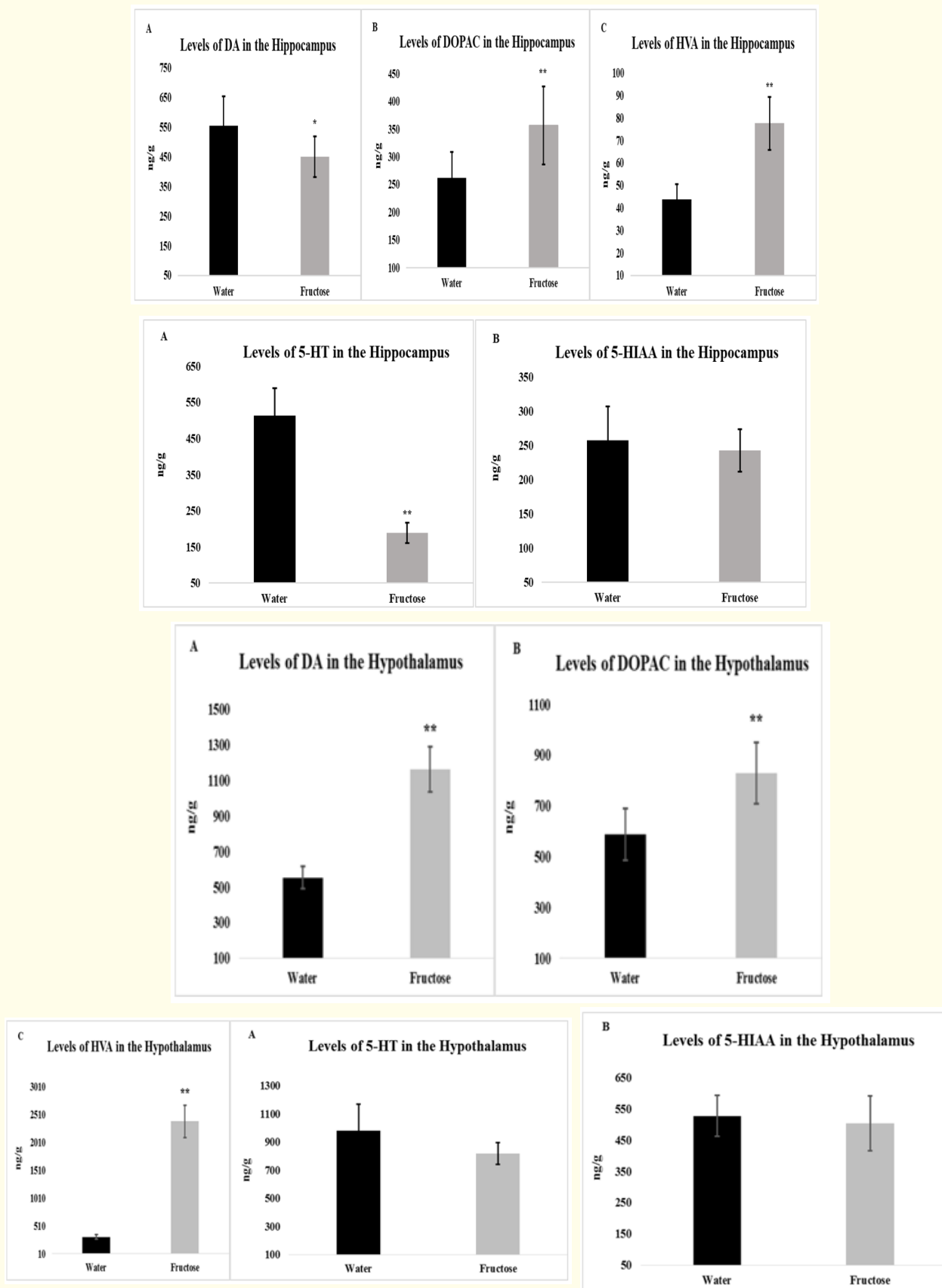


Figure 5-8: Effects of 6-weeks (4g/day) administration of fructose on the hippocampal DA (5A), DOPAC (5B), HVA (5C), 5-HT (6A) and 5-HIAA (6B) and hypothalamic DA (7A), DOPAC (7B), HVA (7C), 5-HT (8A), and 5-HIAA (8B) levels. Values are means \pm S.D (n = 8). Significant difference by independent sample t-test: *p < 0.05, **p < 0.01 from respective water-treated.

Discussion

The present study was conducted to see whether long term consumption of fructose produces greater weight gain. However, we found that administration of fructose for 6-weeks decreased body weight gain as compared to water treated controls. Interestingly the treatment was found to be anxiolytic and resulted in an enhancement in learning and memory, but reference memory was impaired. In view of a role of hippocampal and hypothalamic DA and 5-HT [17,25] in anxiety learning/memory and feeding, the metabolism of these neurotransmitters in the hippocampus and hypothalamus were also determined. Our results showed that an increase in DA turnover and decrease in 5-HT via hippocampus were involved in the memory-enhancing and anxiolytic effect of fructose. Fructose treatment-induced greater DA turnover in the hypothalamus could have contributed to smaller weight gain in these rats.

Studies on the effect of fructose treatment on body weight reported inconsistent results, with no effect on body weight, decreased and increased body weight [26-28]. A previous study reported that Sprague-Dawley rats (200 - 225g) gained more weight after treatment with fructose 23% in drinking solution for 2-weeks. The increase in body weight was associated with higher calorie intake while food intake was decreased [26]. Another study showed that treatment with fructose solution (20%) for 6-weeks did not produce significant body weight changes [28].

In our study animals treated with fructose exhibited reduced body weight gain as compared to water treated control animals, which was associated with a decreased food intake, but the total calorie intake was comparable with control group. Numerous studies show a role of 5-HT, acting via hypothalamic appetite centers in the energy homeostasis and body mass index regulation [14,21]. In this context, the serotonin metabolism in the hypothalamus was determined in the rats treated fructose. Contrary to the previous findings, that high fructose consumption interfere with the L-tryptophan metabolism subsequently reducing serotonin biosynthesis [29], we found that metabolism of serotonin in the hypothalamus was not changed in fructose treated rats. The reduced body weight gain in the present study, however cannot explained in terms of steady 5-HT levels in the hypothalamus.

The role of hippocampal 5-HT and DA neurotransmission is well established in many neurobiological studies in anxiety and memory function [30-33]. These studies showed that changes in hippocampal dopaminergic transmission are associated with hypoactivity and cognitive dysfunction [34,35]. Bernabeu, *et al.* 1997 reported enhanced memory retention by the bilateral administration of D1/D5 receptor agonist into the dorsal hippocampus [36]. Intrahippocampal administration of D1 and D2 receptor agonist and systematic dopamine agonist also improved learning acquisition and spatial memory [37,38]. Brain dopamine metabolism is therefore determined in the hippocampus of rats receiving fructose treatment. We have found that turnover rate of dopamine was increased in the hippocampus or hypothalamus and the levels of dopamine were attenuated and raised in the hippocampus and hypothalamus. A similar observation was found when male C57BL/6J mice of 29-days was treated with 18% fructose diet for 11-weeks [39], however Jimenez, *et al.* 2018 showed reduced hippocampal weight and cellular plasticity markers in rats treated with 8% and 15% fructose for one week [40]. Moreover, the enhanced DA neurotransmission was associated with increased exploratory activity in the OF and greater portion of time pass in the open arm of the EPM test. Our findings are consistent with previous reports which showed that rat submitted to long term honey or sucrose treatment reduced anxiety-like behavior [41].

Numerous evidences showed that anxiety and cognition interact both at behavioral and neuronal level [17,25]. Reduced levels of anxiety, enhance performance in cognitive tests, however, increased anxiety impair cognition [25]. In the present study animals (180 - 220g) receiving fructose treatment for 5-weeks were used to evaluate activity in the MWM test in an experimental model of three days. Our results showed reduced time to reach the platform, both after the 3 and 24-hs, but reference memory, monitored after 36-hs of training in the absence of the platform, showed mixed effects. Both, latency time to reach the reference quadrant and time passed at that quadrant were decreased in the fructose treated rats. Thus, consumption of fructose in pharmacological doses improves the navigational ability of the rats as well as retention competency, but impair reference memory. We suggest that increased DA turnover and the decreased 5-HT neurotransmission via hippocampus is involved in the anxiolytic and mixed effects on memory in fructose treatment.

Conclusions

In the present study, we report that consumption of fructose, not added to food, do not produce obesity. Conversely, body weight gain is reduced by the treatment. Moreover, the treatment is anxiolytic and produces mixed effects on learning and memory. Enhanced DA neurotransmission via the hippocampus and hypothalamus may contribute to, respectively, weight gain reducing and anxiolytic effects of fructose. It suggests that greater consumption of fructose added food products, if linked with obesity, is not due to fructose but due to high palatability of the food product. Fructose in pharmacological doses may be useful in treating obesity and reducing anxiety.

Conflict of Interest

No potential conflict of interest was reported by the authors.

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