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Original Research Article

Biosynthesis of Serotonin in the Brain of Rats under Conditions of Obesity Induced by Compatible Consumption of High Calorie Diet and 10% Fructose Solution as a Possible Target for Obesity Prevention

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ABSTRACT

Background: Obesity becomes global epidemic. The most common model of obesity is the consumption of high calorie feed within a certain time. Serotonin is a neurotransmitter which can be involved in central mechanisms which control food intake. The aim of the present work was to study the features of functioning of the main indicators of serotonin metabolism in experimental obesity, which was induced by the consumption of high-calorie diet and 10 % fructose solution.

Results: We have shown that consumption of high-calorie diet and 10 % fructose solution leads to changes in food behavior and the development of obesity in rats, as evidenced by changes in key physiological and biochemical parameters (body weight had increased by 18% vs controls ($p < 0.05$); Body mass index and Lee index and visceral fat mass had increased ($p < 0.05$); the content of uric acid significantly increased ($p < 0.05$), in comparison with controls). Under the consumption of high-calorie diet and 10 % fructose solution, the content of tryptophan, serotonin significantly decreased ($p < 0.05$). Studies have shown an increase of monoaminoxidase activity by 37 % ($p < 0.05$) and decrease of tryptophan hydroxylase, tryptophan decarboxylase activity in the brain of rats with obesity.

Conclusions: Serotonin plays an important role in the control of food intake and body weight. Greater understanding of serotonergic mechanisms affecting food intake is likely to lead to more efficacious serotonin based pharmacotherapies to aid in appetite control in obese individuals.

Keywords: Obesity; High calorie diet; 10% fructose solution; Animal model; Serotonin; Brain.

INTRODUCTION

Obesity is a complex condition, one with serious social and psychological dimensions, that affects virtually all age and socioeconomic groups and threatens to overwhelm both developed and developing countries. Obesity has reached epidemic proportions globally; about 1.7 billion people on the planet are overweight; at least 2.8 million people dying each year as a result of being overweight or obese. [1] Contrary to conventional wisdom, the obesity epidemic is not restricted to industrialized societies. Overweight and obesity are major risk factors for a number of chronic diseases, including type 2 diabetes mellitus, cardiovascular diseases, hypertension, dyslipidemia and also have an increased risk of developing some types of cancer. [1,2] Thus, World Health

Organization has declared obesity a global epidemic and took it under control.

Obesity is caused by a constellation of factors including excessive energy intake, insufficient energy output, genetic predisposition, low fat oxidation rate, low sympathetic activity, low plasma leptin level, environment favoring weight gain, psychologic stressors and lower socioeconomic status. [3]

Obesity is a multifactorial, heterogeneous disease. The factors that determine the development of obesity are: genetic; demographics (age, gender and ethnicity); socio-economic (education, occupation, marital status); psychological; behavioral (diet, physical activity, alcohol consumption, smoking and stress). Given the data of multiple factors in the pathogenesis of obesity no doubt that a study of various experimental models of the disease, which would have answered pathogenic levels of the disease in humans is an actual and could be the basis for finding promising new drugs, ways of correcting cognitive and motor disorders which occur in conditions of obesity.

The most common model of obesity is the consumption of high calorie feed within a certain time. The limited evidence indicates that hyperinsulinemia and hyperleptinemia are present in obese animals whether on an HFD or HCD, [4-6] while dietary fat is a critical stimulus for development of hyperglycemia as well as hyperphagia. [7] In contrast, sucrose- or starch-rich diets reveal an increased carbohydrate metabolism in muscle in obese rats, which is not evident in obese animals on HFD. [8,9]

Fructose is an isomer of glucose - one of the most common types of natural sugar. According to the literature data, fructose is the one of the links in the chain of biochemical reactions that leads to weight gain and the development of other features of obesity. [10,11] Perhaps the recent years rapid spread of obesity in the population of developed countries is explained by the fact that bakers use large amounts of fructose sweeteners. [12] Exposure to fructose was accelerated by the introduction of high fructose corn syrup. High fructose corn syrup is made by converting glucose into fructose using bacterial enzymes and then diluting the fructose to provide the commercially available high fructose corn syrup solutions that have 55% or 42% fructose. [13]

In the present study we have fed rats a diet high in saturated fats and simple sugars, and supplemented their water with high-fructose syrup.

Animal studies have shown that high-calorie diets impair the structure and function of the hippocampus, a brain region critical for learning and memory. [14-19] The adverse effects of high calorie diets on learning and memory have been associated with impaired hippocampal synaptic plasticity and neurogenesis, [20,21] suggesting that the hippocampus may be particularly sensitive to changes in dietary energy intake. [22]

Serotonin or 5-hydroxytryptamine (5-HT) is a small indolamine (MW 176.2) widely distributed throughout the animal (from ascidies to human) and plant kingdoms. [23-28] Among the large variety of chemical messengers acting in nerve cell signaling, 5-HT is the focus of much interest due to its implication in almost every physiological function (eating, reward, thermoregulation, cardiovascular regulation, locomotion, pain, reproduction, sleepwake cycle, memory, cognition, aggressiveness, responses to stressors, emotion, and mood) and in several human pathologies (restless legs syndrome, [29] sudden infant death syndrome, [30,31] autism, [32] headache, [33] insomnia, [34] anxiety, [35] depression, [36] anorexia, [37,38] schizophrenia, [39]

Parkinson's disease [40] and Alzheimer's disease [41,42]).

In the brain, neuron subpopulations have a set of enzymes permitting the two-step synthesis of 5-HT from its precursor tryptophan. 5-HT is synthesized from L-tryptophan by hydroxylation via the rate-limiting enzyme, tryptophan hydroxylase (TPH; EC 1.14.16.4) and decarboxylation of 5-HTP by aromatic L-amino acid decarboxylase (AADC; EC 4.1.1.28) to 5-HT. TPH has been shown to exist in two forms: TPH1, which is present in several tissues, and TPH2, which is a neuron-specific isoform. [43]TPH is present in the brain mostly in its second isoform, TPH2. [44-45] In the nervous system, 5-HT is mainly metabolized by the monoamine oxidase (MAO; EC1.4.3.4) and a 5-HT half-life of only a few minutes is reported. [46] This enzyme catalyzes the oxidative deamination of serotonin by converting it into 5-hydroxy-3-indolacetaldehyde (5-HIAL), which is further metabolized into 5-hydroxy-3-indolacetic acid (5-HIAA). [47] The aim of the present work was to study the features of functioning of the main indicators of serotonin metabolism in experimental obesity, which was induced by the consumption of high-calorie diet and 10 % fructose solution.

MATERIALS AND METHODS

Research was conducted in compliance with the standards of the Convention on Bioethics of the Council of Europe's 'Europe Convention for the Protection of Vertebrate Animals' used for experimental and other scientific purposes' (1997), the general ethical principles of animal experiments, approved by the First National Congress on Bioethics Ukraine (September 2001) and other international agreements and national legislation in this field. Animals were kept in a vivarium that was accredited in accordance with the 'standard rules on ordering, equipment and maintenance of experimental biological clinics (vivarium)'. Instruments to be used for research are subject to metrological control.

Animals and Housing Conditions:

We included 30 Wistar male rats and divided to 2 groups of 15 animals each. The animals of each experimental group were individually housed in polypropylene cages in an environmentally controlled clean air room, with a temperature of 22±3C, a 12 h light/12 h dark cycle and a relative humidity of 60±5%.

Animals and Diet:

Rats of group 1 (Control) were given water ad libitum and were fed by a standard chow during 70 days of the experimental period. Food and water consumption were measured daily at the same time (09:00 to 10:00 h) and body weights were determined once a week.

Rats of group 2 (HCD_Fr10) were fed by a high-carbohydrate diet, which contained: standard chow (60%), lard (10%), eggs (10%), sucrose (9%), peanut (5%), dry milk (5%), vegetable oil (1%) 48 and received ad libitum 10% sucrose in drinking water [49] during 70 days of the experimental period. Food and water consumption were measured daily at the same time (09:00 to 10:00 h) and body weights were determined once a week.

Biochemical, Anthropometrical and Nutritional Determinations:

Male rats from two experimental groups were weighed and body length of all animals was measured. Body mass index (BMI) (the ratio of body weight (g) of rats to the square of the body length (cm2)) was calculated. [50] The parameter of obesity was obtained by Lee index for each male rat. This index was defined as the cube root of body weight (g) x 10 / nasoanal length (cm), for which a value equal to or less than 0.300 was classified as normal. Rats presenting values higher than 0.300 were classified as obese [51,52] and included in this experiment.

After 70 days of the experimental period the animals were sacrificed. The rats' blood was collected in tubes, brain was removed and weighed.

The tryptophan content was determined in brain using ion-exchange chromatography and fluorescence methods which were described previously. [53-55] The 5-hydroxytryptophan content was determined in brain using fluorescence method which was described previously. [56] Determination of tryptophan hydroxylase activity was performed according to the method recommended in [57] Determination of tryptophan decarboxylase activity was carried by the spectrofluorimetric method described previously. [58] MAO activity was estimated according to the method of Krajl (1965), in which the production of 4-hydroxyquinoline from the oxidative deamination of kynuramine is measured. [59]

Statistics:

Statistical analysis of data was carried out by the software package 'Statistica 7.0'. For the analysis of data distribution type, Shapiro-Wilks criterion was used. As the data were normally distributed, we used Student's t test for independent samples. Mean values (M) and standard deviations (SD) were calculated. Significant difference was considered at $p \leq 0.05$.

RESULTS

Table 1 shows the general characteristics of animals. There was no significant difference in food intake among the control group (15, 7±1,283) and in the group of rats that were on the combined consumption of 10% solution of fructose and high-calorie diet (15, 6±2,875), although the control group had a lower calorie intake. It was found that after 10 weeks in group of animals that were on the combined consumption of 10% solution of fructose and high-calorie diet, fluid intake was significantly higher in comparison with control animals in 1.6 times (Control 15, 4±1,590 and HCD-FR10 24,7±5,173 ml/day, $p < 0.05$).

Table 1. General characteristics of animals

	Control	HCD-FR10
Food consumption (g/day)	15,7±1,283	15,6±2,875
Fluid intake (ml/day)	15,4±1,590	24,7±5,173*
Initial body weight (g)	142±2,081	145±9,377
Final body weight (g)	229±1,154#	271±18,126*/#
BMI (g/cm^2)	0,49±0,01	0,59±0,02*
Lee index	0,28	0,34

Data are shown as the mean ± SD of 15 animals; asterisk (*), $p < 0.05$ in comparison with control group

The initial weight of the animals in the control group was 142±2,081 g and the final body weight was 229±1,154 g. It was found that after 10 weeks of consumption HCD-FR10 body weight of rats was significantly higher in comparison with initial weight (initial weight 145±9,377 g and final weight 271±18,12 g, $p < 0.05$). The increase in body weight after 10 weeks of experiment was 126 g compared with the initial weight of the animals in the group. The calculation of body mass index and Lee index suggested the development of obesity in HCD-FR10 group.

Analysis of the content of uric acid in serum in rats showed an increase of this indicator in 1.5 times (Control 125,10±12,7 μmol/l and HCD_Fr10 185,86±23,93 μmol/l, $p < 0.05$) in HCD-FR10 group compared to control animals (Figure 1).

The level of tryptophan in the brain of rats with HCD_Fr10-induced obesity has been increased in 3.1 times (Control 54,792±6,799 mkg/g and HCD_Fr10 17, 708±5, 6111, $p < 0.05$) (Figure 2A).

The research of a key and rate-limiting enzyme of serotonin biosynthesis - tryptophan-hydroxylase activity in the brain of rats with the experimental model of obesity has shown a decrease of enzyme activity by 28 % in comparison with the values of the control group (Figure 3).

The analysis of the brain 5-HTr content has shown a decrease of this indicator in 1.9 times (Control 157.69±24.653 units/g and HCD_Fr10 85.19±16.558 units/g, $p < 0.05$) in HCD-FR10 group compared to the intact animals (Figure 2B). Enzyme that catalyzes the synthesis of the second step - 5-hydroxytryptophan decarboxylation and its conversion to serotonin, is an aromatic L-amino acids decarboxylase.

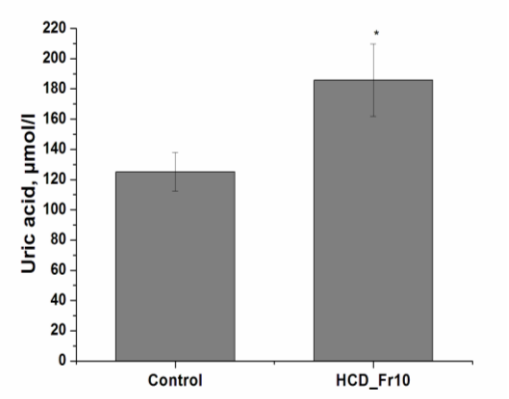

Figure 1. Amount of uric acid (µmol/l) in serum of rats with HCD_Fr10-induced obesity
Data are shown as the mean ± SD of 15 animals; asterisk (*), $p < 0.05$ in comparison with control group

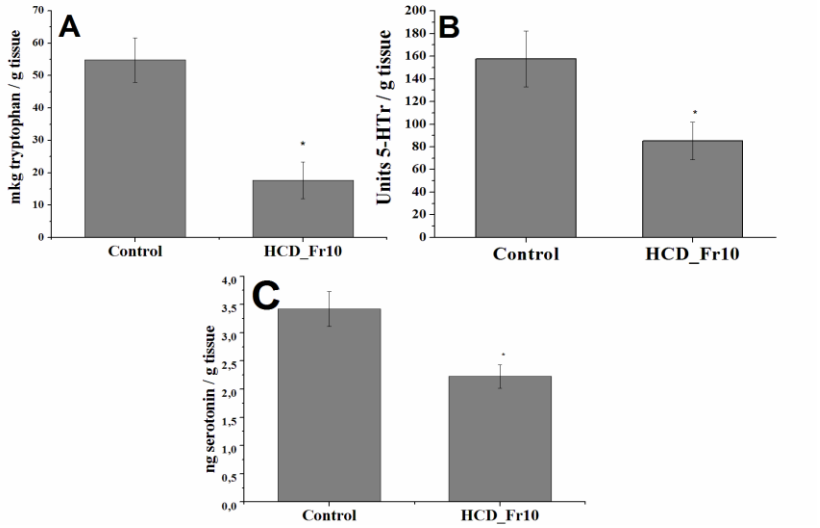

Figure 2. Content of (A) tryptophan (µg/g tissue), (B) 5-hydroxytryptophan (units/ g tissue), (C) serotonin (ng/g tissue) in brain tissue of rats with HCD_Fr10-induced obesity Data are shown as the mean ± SD of 15 animals; asterisk (*), $p < 0.05$ in comparison with control group

According to the data presented in Figure 3 tryptophan-decarboxylase activity has been decreased by 51 % in the rats under joint consumption of high-calorie diet and 10% solution of fructose.

Studies have shown a decrease in the content of serotonin in 1.5 times (Control 3.41±0.308 units/g and HCD_Fr10 2.22±0.207 units/g, $p < 0.05$) in the brain of rats under joint consumption HCD and 10% solution of fructose compared with the control group of animals (Figure 2C).

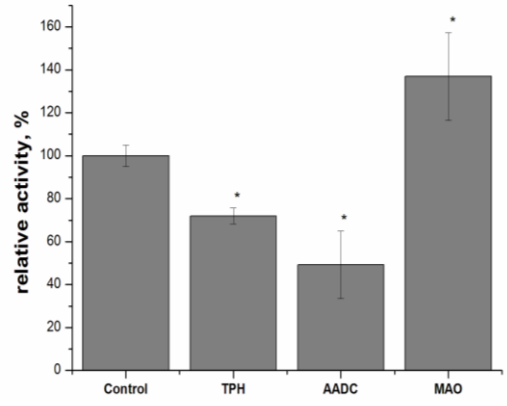

Figure 3. Tryptophan hydroxylase (TPH), amino acid decarboxylase (AADC), monoamine oxidase (MAO) activity in brain tissue of rats with HCD_Fr10-induced obesity

Studies have shown an increase of monoaminoxidase (MAO) activity by 37 % in the brain of rats with experimental obesity compared with the values of the control group (Figure 3).

Data are shown as the mean ± SD of 15 animals; asterisk (*), $p < 0.05$ in comparison with control group

DISCUSSION

Data confirm the findings that the compatible consumption of high-calorie diet rats and 10% fructose solution induces the development of obesity in adult animals and is a model of obesity in rodents. [60,61]

We consider the joint consumption of high-calorie diet rats and 10% fructose solution in this article. Fructose is distinct from other sugars in its ability to cause intracellular ATP depletion, nucleotide turnover, and the generation of uric acid. We've decided to explore the content of uric acid in the blood serum of experimental animals. An elevated serum uric acid is one of the best independent predictors of diabetes and commonly precedes the development of both insulin resistance and diabetes. [62] An elevated uric acid also independently predicts the development of fatty liver, [63] obesity, [64] hypertension, [65] and elevations in C-reactive protein. [66] Uric acid produced from the nucleotide turnover that occurs during the phosphorylation of fructose to fructose-1-phosphate results in the generation of mitochondrial oxidative stress, which causes a decrease in the activity of aconitase in the Krebs cycle. As a consequence, the ACO2 substrate, citrate, accumulates and is released to the cytosol where it acts as substrate for TG synthesis through the activation of ATP citrate lyase and fatty acid synthase. A number of conditions associated with hyperuricemia are also associated with increased risk for insulin resistance or diabetes, including chronic lead intoxication and gestational diabetes mellitus. Many drugs associated with insulin resistance can also cause a hyperuricemia, such as calcineurin inhibitors and thiazide diuretics. Thus, hyperuricemia is a risk factor for obesity.

The central mechanisms which control food intake involve many CNS regions and including different neurotransmitters and neuropeptides. One of these neurotransmitters, is serotonin (5-hydroxytryptamine). Serotonin influences both brainstem reflex centres and hypothalamic integratory centres involved in food intake control. A significant amount of studies have been conducted to characterize the interactions between serotonin and this food intake neurocircuitry.

Considering the literature data about relationship between the biogenic amine neurotransmitter serotonin and food intake we have studied the biosynthesis of serotonin in rats with obesity. Analysis of the results has shown a deviation in the brain serotoninergic system functioning in rats with experimental obesity caused by HCD_Fr10. Taking into account the literature data about relationship between the biogenic amine neurotransmitter serotonin and food intake we have investigated the biosynthesis of serotonin in rats with obesity.

These results have been confirmed by the literature data, which shows the low levels of tryptophan in rats with insulin resistance, type 2 diabetes. Also, in previous studies, we have shown lower content of tryptophan in the brain of rats with obesity induced by consumption of high-calorie diet. [67]

The research of a key and rate-limiting enzyme of serotonin biosynthesis - tryptophan-hydroxylase activity in the brain of rats with the experimental model of obesity has shown a decrease of enzyme activity by 28 % in comparison with the values of the control group (Figure 3). This

decrease in activity of TPH is consistent with the results that we obtained earlier in rats with type 2 diabetes and obesity induced by HCD consumption. [67]

Decreased activity of the TPH can be associated with a lowering level of the substrate of the enzymatic reaction - tryptophan and also with a reduction of the bioavailability of a enzyme cofactor - tetrahydrobiopterin (BH4), the biosynthesis of which, as shown in literature data, is lowered due to the development of oxidative stress in obese patients. [68]

Decrease in 5-HTr is correlated with a decrease in the activity of TPH. The value of this indicator, which is a precursor to serotonin, it is very important because its involvement in the regulation of feeding behavior of the organism; 5-HTr consumption as biological additives used clinically as an antidepressant and appetite suppressant. Lowering of the level of 5-HTP is observed at the development of obesity, clinical depression, as well as hypothalamic syndrome. [69] Reduced tryptophan decarboxylase activity may be associated with the development of the enzyme cofactor deficiency - vitamin B6 deficiency that is often prevalent in obese patients. [70,71] It is known that the aromatic L-amino acids decarboxylase is involved in the biosynthesis of the neurotransmitter dopamine, by decarboxylation of its precursor - dihydroxyphenylalanine (L-dopa). The reduction in the activity of this enzyme may lead to a combined deficiency of catecholamines and serotonin, which in turn may lead to the development of some neurological disorders such as: hyperphagia, hypothermia, depression, dementia, pathological aggression, etc. [7267]

Decreased concentration of serotonin may be due to several reasons: firstly, with a decrease in production of a neurotransmitter, which may be the result of an imbalance in the system of its synthesis, and a violation of metabolic processes aimed at the maintenance of physiological levels of serotonin in the body. Second, reduction of this parameter may be associated with the increased catabolism of serotonin. In its turn a violation of serotonergic transmission, resulting in a decrease in serotonin levels in the brain, is one of the factors in the formation of depressions, and can be considered as one of the main causes of obesity and type 2 diabetes mellitus. [72]

Since the decrease in the concentration of serotonin in the brain in rats of the experimental group can be connected not only to a decrease in production of neurotransmitter, but also to enhancement of its catabolism process, we have defined the activity of the enzyme monoamine oxidase (MAO), which provides the degradation of serotonin through oxidative deamination.

Increased MAO activity may be associated with excessive activation of the enzyme, which in turn may lead to a decrease in the pool of biogenic amines, especially serotonin. Violation of this enzyme activity may be a cause of depression and progression of obesity. [68]

CONCLUSION

Serotonin plays an important role in the control of food intake and, consequentially, body weight. Greater understanding of serotonergic mechanisms affecting food intake is likely to lead to more efficacious serotoninbased pharmacotherapies to aid in appetite control in obese individuals.

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Abbreviations

HCD: high-carbohydrate diet; Fr_10: 10% solution of fructose; 5-HT: 5-hydroxytryptamine; MAO: monoaminoxidase; TPH: tryptophan hydroxylase; AADC: aromatic L-amino acid decarboxylase; 5-HTP: 5-hydroxytryptophane; 5-HIAL: 5-hydroxy-3-indolacetaldehyde; 5-HIAA: 5-hydroxy-3-indolacetic acid; BH4: tetrahydrobiopterin; BMI: body mass index.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

KTP performed experiments and statistical analysis of obtained data and prepared the article. KVV, KLI performed experiments and analysis of the study, did the literature review in part of the discussion, formulated prospects and performed the final article drafting. OLI did the organization, literature review and analysis of the study. All authors read and approved the final manuscript.

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