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Research Article

Vascular responses disrupted by fructose-induced hyperinsulinemia improved with delta-9-tetrahydrocannabinol

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Abstract

Objectives: In recent years, cannabinoids have been shown to have beneficial effects on diabetic vascular complications. Vascular complications due to fructose-induced hyperinsulinemia (HI) and diabetic vascular complications have similar mechanisms. The aim of this experimental study was to observe whether the cannabinoid agonist delta-9-tetrahydrocannabinol (THC) has an ameliorating effect on fructose-induced HI and vascular responses in the aortic ring of rats with HI.

Methods: A total of 24 rats were categorized into 4 groups: control (standard food pellets and water), HI (water containing 10% fructose provided for 12 weeks), THC (1.5 mg/kg/day intraperitoneal administration for 4 weeks), and THC+HI. Body weight was measured again on the last day of the study and the serum insulin level was measured with an enzyme-linked immunosorbent assay. The acetylcholine (ACh) maximum relaxant effect in aortic rings pre-contracted with noradrenaline (NA) was evaluated.

Results: The body weight of THC and THC+HI groups was lower compared with that of the controls ($p<0.01$). Increased insulin level as a result of fructose consumption decreased with THC administration ($p<0.01$) while the glucose level increased in all other groups compared with the control group ($p<0.01$, $p<0.05$). The NA Emax value decreased in the group receiving THC treatment ($p<0.01$). The increased ACh pD2 value in the HI groups also decreased in the THC treatment group ($p<0.0001$). The decreased maximum inhibition value in the HI group increased significantly with THC administration ($p<0.001$).

Conclusion: THC demonstrated beneficial effects on fructose-induced HI. THC improved ACh-induced endothelial-dependent relaxation in HI rat aortic rings.

Keywords: Endothelial-dependent relaxation, hyperinsulinemia, tetrahydrocannabinol, vascular response

Insulin induces glucose uptake in many metabolic tissues to maintain glucose homeostasis under physiological conditions [1]. It has been established that vascular changes occur due to hyperinsulinemia (HI) , which is a symptom of insulin resistance, and is therefore an important cardiovascular risk factor [2]. Recent studies have shown that high consumption of refined carbohydrates increases the risk of developing insulin resistance [3]. A high-fructose diet disrupts the function of tissues and organs and supports the development process of metabolic syndrome and insulin resistance [4]. Fructolysis,

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or fructose metabolization, largely occurs in the liver, producing primary metabolites and by-products, such as glucose, very low-density lipoprotein-triglyceride, lactate, free fatty acid, and uric acid [5].

Delta-9-tetrahydrocannabinol (THC), the most important psychoactive ingredient of *Cannabis sativa*, acts through cannabinoid-1 (CB1) and cannabinoid-2 (CB2) receptors [6]. Recent preclinical and clinical studies have shown that cannabinoid receptor activation is related to weight gain and insulin resistance, and that cannabinoids have beneficial effects for increased energy intake, impaired glucose, and lipid metabolism [7]. In addition, cannabinoids have demonstrated beneficial effects on diabetes and lipid metabolism by activating peroxisome proliferator-activated receptors (PPARs) [8]. PPARs are part of the nuclear receptor superfamily, and involved in the regulation of lipid metabolism, insulin sensitivity, glucose homeostasis, and hepatic expression of peroxisomal enzyme, and PPARγ agonists are used to reduce blood glucose levels and treat insulin resistance and type 2 diabetes mellitus (T2DM) [9].

Recent research has shown that cannabidiol caused vasorelaxation of the human mesenteric artery and may be an effective treatment for diabetes-related cardiovascular complications [10]. Cannabinoid receptors may be a novel pharmacological target for restoration of cardiovascular function [11]. Both CB1 and CB2 receptors are expressed in endothelial and vascular smooth muscle cells. However, the effect of cannabinoids on the vessels does not always occur through the cannabinoid receptors [7]. PPARs contribute to the relaxant effect of cannabinoids on the vessels [12]. The objective of this research was to explore whether the non-specific cannabinoid receptor agonist THC improved suitable fructose-induced HI and to examine changes in the vascular response caused by HI.

Materials and Methods

Subjects

A total of 24 male Sprague-Dawley rats aged 8-10 weeks were used in this study. The animals were housed with a 12/12-hour light-dark cycle and provided with standard feed and water. Four groups were formed with random selection: control (n=6), HI (n=6), THC (n=6), and THC+HI (n=6). The study was approved by the Istanbul University Animal Research Local Ethic Committee (2015/66). The HI group was given drinking water containing 10% fructose for 12 weeks, and THC was administered intraperitoneally at 1.5 mg/kg for the last 4 weeks, according to the study method of Beydogan et al. [13]. On the last day of the study, all of the animals fasted overnight and body weight was recalculated. Anesthesia was administered before blood samples were taken.

Drugs

The THC product used in this study was THC-1098 from THC Pharm GmbH, Frankfurt, Germany. All other chemicals used were purchased from Merck KGaA, Darmstadt, Germany.

Glucose and insulin level measurement

The fasting blood glucose level was measured with a glucometer using blood samples collected from the tail of the rats (Accu-Chek; Roche Diagnostics, Basel, Switzerland). The blood samples were centrifuged at 2000 g for 15 minutes and the serum insulin level was evaluated with an enzyme-linked immunosorbent assay commercial kit (Rat/Mouse EZRMI-13K; Merck KGaA, Darmstadt, Germany).

Experimental procedures for vascular assessment

Following administration of anesthesia with sodium thiopental, the experimental animals were sacrificed and the thoracic aorta was immediately removed. The aortas were kept in Krebs-Henseleit solution (KHS; sodium chloride: 119 nM, potassium chloride: 4.70 nM, magnesium sulfate: 7 nM, water: 1.20 nM, potassium dihydrogen phosphate: 1.20 nM, calcium chloride: 2.50 nM, sodium bicarbonate: 25 nM, glucose: 11.1 nM). The aorta was cut into 3-4 mm rings and fixed with 1 g resting tension in an isolated organ bath (4050; Ugo-basile, Gemonio, Italy) with 25 mL KHS, ventilated at 37°C (95% molecular oxygen and 5% carbon dioxide). A force-displacement transducer (MP36; Biopack Systems Inc., Goleta, CA, USA) and integrated Tissue Bath Sysytem (ITBS08, Commat Ltd., Ankara, Turkey) were used to analyze the isolated aortic rings isometrically. After an hour of incubation, a noradrenaline (NA) concentration-response curve was determined by raising the concentration of NA (10^{-9}–10^{-4} mol/L) until there was no further increase in contractile force and maximal cumulative response was observed. Each dose was added following observation of a plateau response. After each aortic ring was submaximally (EC90 10^{-5}) pre-contracted with NA, a cumulative relaxation graph for acetylcholine (ACh) (10^{-9}–10^{-4} mol/L) was created. The thoracic aortic tissue was dried, measured, and weighed at the end of each experiment.

Agonist doses were expressed as base-10 logarithm (M) in the dose-response graph. The sensitivity of agonists was expressed as the negative logarithm of the molar concentration that produces the half-maximum effect (pD2 = -log EC50). The ACh relaxation responses were presented as the maximum percentage inhibition on NA-induced contraction (Inh_{max} %). The NA contraction responses were expressed as maximum response (E_{max}). Contractile-relaxation responses were calculated as a rise or fall of tension in milligrams per aorta (mg tension/mg wet weight=mg/mg ww).

Statistical analysis

The statistical calculations were performed using Prism 9.0.0 software (GraphPad Software, San Diego, CA, USA). Statistical analyses were performed using two-way analysis of variance (ANOVA), followed by Tukey's multiple comparison test for isolated organ bath experiments. pD_2 (M), E_{max} and Inh_{max} data were calculated using non-linear regression analysis. Serum insulin level, glucose level, and body weight data were calculated using Kruskal-Wallis non-parametric ANOVA, followed

by the Mann-Whitney U test. All of the data were presented as the mean±SEM to display variations in groups. P<0.05 was considered statistically significant.

Results

Body weight

A comparison of the final body weight of all of the experimental groups is displayed in Figure 1. The body weight of all of the subjects was measured before and after THC treatment. There was no statistically significant difference in body weight in the control group or the HI group; fructose intake did not have a direct effect on the weight of the rats. However, there was a significant decrease in body weight of animals in THC group compared with the control and the HI group (p<0.01) and body weight also decreased in HI+THC group compared with the HI group (p<0.01).

Insulin and glucose levels

The serum insulin level of all of the subject groups is displayed in Figure 2. The serum insulin level increased in the HI group compared with the control group and the THC group, while THC administration decreased the insulin level in the HI+THC group (p<0.01).

The blood glucose level of the subjects is presented in Figure 3. The blood glucose level was statistically significant in the control group compared with the HI, THC, and HI+THC groups (p<0.01, p<0.05).

Noradrenaline contractile response

The NA contraction response pD_2 and E_{max} values of all of the groups are displayed in Table 1. Comparison of the NA pD_2 values of the HI group (8.16±0.15 M) and the control group (7.76±0.32 M), and the HI+THC group (8.08±0.20 M) and the THC group (8.49±0.40 M) yielded no statistically significant difference. The E_{max} value was considerably lower in the THC group in comparison with the control group (339.01±43.25 mg/mg ww) and the THC group (240.39±10.31 mg/mg ww) (p<0.01). Similarly, when the HI group (396.14±33.72 mg/mg ww) and the HI+THC group (255.76±17.23 mg/mg ww) were compared, the E_{max} response was considerably lower in the THC treatment group (255.76±17.23 mg/mg ww) (p<0.05).

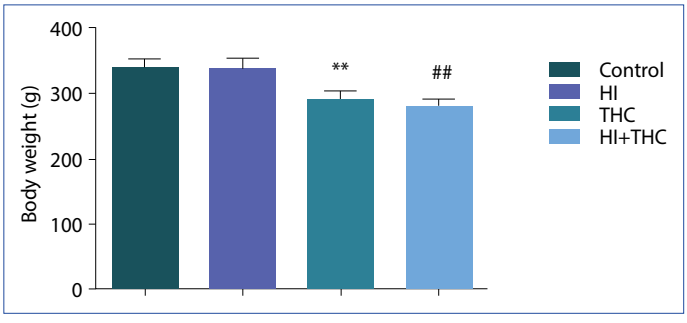

Figure 1. Body weight of experimental groups (n=6 for all groups). **p<0.01, THC group compared with Control and HI groups; ##p<0.01, HI+THC group compared with Control and HI groups. HI: Hyperinsulinemic; THC: Delta^9-tetrahydrocannabinol.

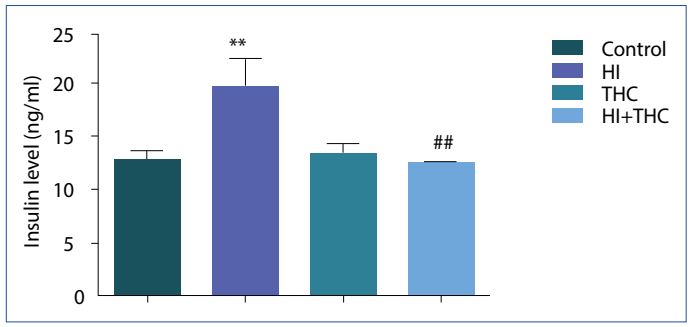

Figure 2. Serum insulin level of experimental groups (n=6 for all groups). **p<0.01, HI group compared with Control group and THC group; ##p<0.01, HI+THC group compared with HI group. HI: Hyperinsulinemic; THC: Delta^9-tetrahydrocannabinol.

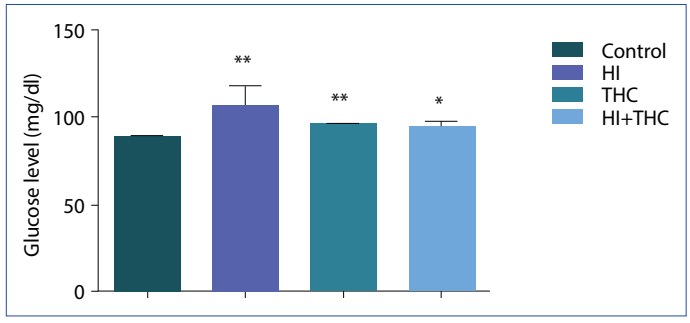

Figure 3. Blood glucose level of experimental groups (n=6 for all groups). ** p<0.01; * p<0.05, Control group compared with HI, THC, and HI+THC groups. HI: Hyperinsulinemic; THC: Delta^9-tetrahydrocannabinol.

Acetylcholine relaxation response

The endothelial-dependent relaxation response (pD_2 and Inh_{max} %) in the rat aortic rings pre-contracted with NA (submaximally, EC90) are shown in Table 2 and the ACh concentration-dependent relaxation response is shown in Figure 4. The Ach pD2 value was significantly greater in the HI group (6.25±1.98 M) compared with the control group (5.87±0.74 M) (p<0.0001) and the HI+THC group (5.62±4.90 M) (p<0.0001). The ACh Inh_{max} value was significantly lower in the HI group (13.60±6.24%) in the comparison with the control group (93.60±0.16%) (p<0.0001), while the HI+THC group result (70.25±8.42%) was greater than that of the HI group (13.60±6.24%) (p<0.001). Vascular responses were better in the THC treatment group than in the HI group (p<0.05).

Discussion

HI, or an abnormally high level of insulin, has become more prevalent due to increased consumption of refined foods

Table 1. pD_2 and E_{max} values for noradrenaline-induced contraction responses

	Noradrenaline	
	E_{max} (mg/mg ww)	pD_2 (M)
Control	339.01±43.25	7.76±0.32
HI	396.14±33.72	8.16±0.15
THC	240.39±10.31**	8.49±0.40
HI+THC	255.76±17.23*	8.08±0.20

Values are mean±SEM, **p<0.01 THC group compared with HI group and control group, *p<0.05 HI+THC group compared with HI group (n=6 for all groups). E_{max}: Maximum response, HI: Hyperinsulinemic, pD_2: Agonist sensitivity, THC: Delta9-tetrahydrocannabinol

Table 2. pD_2 and Inh_{max} values for acetylcholine-induced relaxation responses

	Acetylcholine	
	Inh_{max} (%)	pD_2 (M)
Control	93.60±0.16	5.87±0.74
HI	13.60±6.24****	6.25±1.98****
THC	72.65±8.14	7.68±0.51
HI+THC	70.25±8.42****	5.62±4.90****

Values are mean±SEM, ****p<0.0001 Control group compared with the HI group, ***p<0.001 HI group compared with the HI+THC group (n=6 for all groups). pD_2 and Inh_{max} of ACh decreased in the fructose-induced HI group and improved with THC treatment. ACh: Acetylcholine, HI: Hyperinsulinemic, Inh_{max}: Maximum relaxation, pD_2: Sensitivity, THC: Delta^9-tetrahydrocannabinol

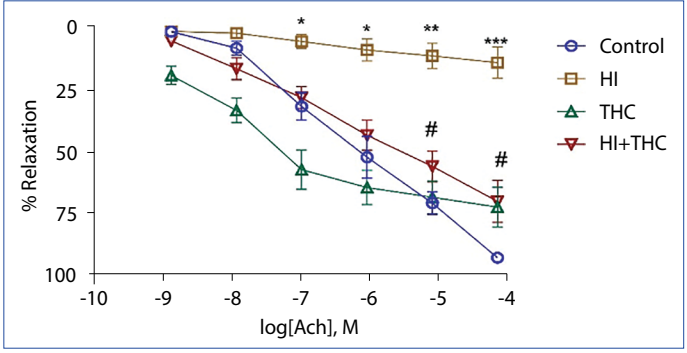

Figure 4. ACh relaxation response of experimental groups (n=6 for all groups). *p<0.05; **p<0.01; ***p<0.001 HI group compared with Control group. #p<0.05 HI group compared with HI+THC groups. ACh: Acetylcholine, HI: Hyperinsulinemic, THC: Delta9-tetrahydrocannabinol.

containing high fructose, and the associated cardiovascular changes are important risk factors that are becoming common all over the world. Cannabinoids have been shown to have a useful effect in diabetes treatment and its associated complications. In this study, THC, the principal psychoactive component of *Cannabis sativa*, was tested to examine vascular changes in the aorta ring of rats given high-fructose water.

Although weight gain has been observed due to high consumption of fructose in experimental metabolic disease models, there is not always a correlation between fructose intake and body weight [13]. Our results revealed no significant change in body weight due to fructose intake.

The endocannabinoid system is one of the important neuromodulatory systems that influence appetite and food intake. Stimulation of the endocannabinoid system with synthetic or herbal-derived ligands such as THC typically leads to an increase in food intake in both humans and animals [14]. The CB1 receptor has been shown to mediate the effect of THC on nutritional intake and weight [15] and this effect has been suppressed by the CB_1 receptor antagonist SR 141716 (rimonabant) [16]. It has been observed that chronic THC intake decreased energy need in animals, suppressed nutrition, and caused weight loss [17]. In our study, THC did not lead to weight gain in any of the experimental animals; on the contrary, weight loss was observed. This may have been a result of the duration and dose of THC.

Recent research has indicated that a high-fructose diet can change certain metabolic conditions in humans and experimental models, causing diseases such as hypertriglyceridemia, obesity, and high blood pressure, and facilitate the development of HI, insulin resistance, and hyperglycemia [18]. In our study, there was a meaningful increase in the insulin and glucose levels in the groups that were given fructose compared with the control group, but THC treatment did not significantly reduce the blood glucose level.

CB_1 receptor signaling in adipose tissue and the liver has been reported to cause obesity and metabolic conditions, such as insulin resistance and dyslipidemia, by increasing fatty acid intake, lipogenesis, and adipogenesis [7]. It was reported in another study that CB_1 receptor blockade reversed obesity-induced insulin resistance [19]. Growing evidence in recent years has indicated that endocannabinoids alter insulin receptor activity by affecting CB_1 receptors expressed in beta cells [20]. In a study using the CB_1 receptor antagonist ibipinabant, β-cell loss was reported to be reduced without affecting body weight [21]. It has also been established that insulin sensitivity in skeletal muscles is reduced by CB_1 receptors using the target phosphoinositide-3-kinase-protein kinase B axis and the rapidly accelerated fibrosarcoma (Raf)-mitogen-activated protein kinase (MEK) 1-2-extracellular signal-regulated kinase 1/2 pathways [22]. However, Beydogan et al. [13] found that the serum insulin level was reduced with cannabinoid receptor partial agonist THC treatment. We found that the glucose level of the HI rats did not significantly change with THC treatment, but THC regulated the increased insulin level in HI rats. It is clear that cannabinoids are potential therapeutic target for insulin resistance, but it is understood that not all the effects of cannabinoids on the insulin signal pathway occur through cannabinoid receptors.

PPARγ, a subtype of the nuclear receptor superfamily, has a significant impact on glycolipid metabolism and insulin resistance. Recent studies have shown that PPARγ activation was very effective in alleviating the effects of T2DM [5]. Research has also shown that THC, which can be a PPARγ agonist, increases the effects of insulin by decreasing the level of tumor necrosis factor alpha [23]. Safer insulin-sensitizing, selective PPARγ-agonist compounds have been developed in the last few years, since thiazolidinedione-group synthetic agonists used in T2DM treatment can result in cardiovascular risk, fluid retention, and hepatoxicity [24].

Cannabinoids have been shown to cause endothelium-dependent relaxation [24, 25]. These results indicate that the ameliorating effect of THC against changes in both insulin resistance and vascular responses may be conducted through PPARγ receptors. The receptor target mediating the endothelium-dependent relaxing effect of cannabinoids in vessels has recently been shown to be PPARs [26].

There is a close relationship between an impaired insulin level and vascular contraction-relaxation responses. In this research, we investigated the effect of THC to improve impaired contraction-relaxation responses in the aorta of rats as a result of HI induced with fructose. Our results demonstrated that 1.5 mg/kg/day intraperitoneal THC administration for 4 weeks improved endothelial-dependent Ach relaxation responses in comparison with the HI group. Chronic THC administration improved the reduced relaxation responses and ACh pD_2 in the aortic rings of rats with fructose-induced HI.

Conclusion

In this preclinical study, we demonstrated that chronic THC administration to HI rats decreased the insulin level without weight gain. THC improved endothelial-dependent relaxation responses. THC application also had the beneficial effect of increased contractile responses to NA in HI rats. Chronic administration of THC did not lead to weight gain in rats, but longer use and higher doses may increase nutrient intake and cause weight gain, thereby worsening the prognosis of HI. The current results revealed possible positive effects of THC and altered vessel responses in an *in vivo* experimental HI model.

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Conflict of Interest: The authors do not have any conflict of interest in the manuscript.

Ethics Committee Approval: The study was approved by the Local Animal Care Ethics Committee, Istanbul University (Approval No. 2015/66).

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Authorship Contributions: Concept – Z.M.C., S.B., S.O., A.G.A.; Design – Z.M.C, S.B., S.O., A.G.A.; Supervision – Z.G.T.S., S.O., A.G.A., S.B.; Funding – None; Materials – C.K., S.O., A.G.A., S.G.; Data collection &/or processing – Z.G.T.S., C.K., S.G.; Analysis and/or interpretation – Z.G.T.S., S.O., A.G.A., Z.M.C.; Literature search – Z.G.T.S., S.O.; Writing – Z.G.T.S. S.O.; Critical review – Z.G.T.S., S.G., A.G.A., S.O., Z.M.C.

References

1. Honka MJ, Latva-Rasku A, Bucci M, Virtanen KA, Hannukainen JC, Nuutila P. Insulin-stimulated glucose uptake in skeletal muscle, adipose tissue and liver: a positron emission tomography study. Eur J Endocrinol 2018;178(5):523–31. [CrossRef]
2. Jia G, DeMarco VG, Sowers JR. Insulin resistance and hyperinsulinaemia in diabetic cardiomyopathy. Nat Rev Endocrinol 2016;12(3):144–53. [CrossRef]
3. Altas M, Var A, Kose C, Ozbilgin K, Arı Z. Endothelial dysfunction in high fructose containing diet fed rats: Increased nitric oxide and decreased endothelin-1 levels in liver tissue. Dicle Med J 2010;37(3):193–8.
4. Borowska M, Czarnywojtek A, Sawicka-Gutaj N, Woliński K, Płazińska MT, Mikołajczak P, et al. The effects of cannabinoids on the endocrine system. Endokrynol Pol 2018;69(6):705–19.
5. Burstein S. PPAR-gamma: a nuclear receptor with affinity for cannabinoids. Life Sci 2005;77(14):1674–84. [CrossRef]
6. Ulugöl A. The endocannabinoid system as a potential therapeutic target for pain modulation. Balkan Med J 2014;31(2):115–20. [CrossRef]
7. Eckardt K, Sell H, Taube A, Koenen M, Platzbecker B, Cramer A, et al. Cannabinoid type 1 receptors in human skeletal muscle cells participate in the negative crosstalk between fat and muscle. Diabetologia 2009;52(4):664–74. [CrossRef]
8. Gruden G, Barutta F, Kunos G, Pacher P. Role of the endocannabinoid system in diabetes and diabetic complications. Br J Pharmacol 2016;173(7):1116–27. [CrossRef]
9. Han L, Shen WJ, Bittner S, Kraemer FB, Azhar S. PPARs: regulators of metabolism and as therapeutic targets in cardiovascular disease. Part II: PPAR-β/δ and PPAR-γ. Future Cardiol 2017;13(3):279–96. [CrossRef]
10. Stanley CP, Hind WH, Tufarelli C, O'Sullivan SE. Cannabidiol causes endothelium-dependent vasorelaxation of human mesenteric arteries via CB1 activation. Cardiovasc Res 2015;107(4):568–78. [CrossRef]
11. Ho C, Martinusen D, Lo C. A Review of Cannabis in Chronic Kidney Disease Symptom Management. Can J Kidney Health Dis 2019;6:2054358119828391. [CrossRef]
12. Horváth B, Mukhopadhyay P, Haskó G, Pacher P. The endocannabinoid system and plant-derived cannabinoids in diabetes and diabetic complications. Am J Pathol 2012;180(2):432–42. [CrossRef]
13. Beydogan AB, Coskun ZM, Bolkent S. The protective effects of Δ9 -tetrahydrocannabinol against inflammation and oxidative stress in rat liver with fructose-induced hyperinsulinemia. J Pharm Pharmacol 2018;71(3):408–16. [CrossRef]

14. Weltens N, Depoortere I, Tack J, Van Oudenhove L. Effect of acute Δ9-tetrahydrocannabinol administration on subjective and metabolic hormone responses to food stimuli and food intake in healthy humans: a randomized, placebo-controlled study. Am J Clin Nutr 2019;109(4):1051–63. [CrossRef]
15. Ogden SB, Malamas MS, Makriyannis A, Eckel LA. The novel cannabinoid CB1 receptor agonist AM11101 increases food intake in female rats. Br J Pharmacol 2019;176(20):3972–82.
16. Radziszewska E, Bojanowska E. Effects of glucagon-like peptide-1 receptor stimulation and blockade on food consumption and body weight in rats treated with a cannabinoid CB1 receptor agonist WIN 55,212-2. Med Sci Monit Basic Res 2013;19:6–11. [CrossRef]
17. Cluny NL, Keenan CM, Reimer RA, Le Foll B, Sharkey KA. Prevention of Diet-Induced Obesity Effects on Body Weight and Gut Microbiota in Mice Treated Chronically with Δ9-Tetrahydrocannabinol. PLoS One 2015; 10(12):e0144270. [CrossRef]
18. Miranda CA, Schönholzer TE, Klöppel E, Sinzato YK, Volpato GT, Damasceno DC, et al. Repercussions of low fructose-drinking water in male rats. An Acad Bras Cienc 2019;91(1):e20170705.
19. Liu J, Zhou L, Xiong K, Godlewski G, Mukhopadhyay B, Tam J, et al. Hepatic cannabinoid receptor-1 mediates diet-induced insulin resistance via inhibition of insulin signaling and clearance in mice. Gastroenterology 2012;142(5):1218–28. [CrossRef]
20. Kim W, Doyle ME, Liu Z, Lao Q, Shin YK, Carlson OD, et al. Cannabinoids inhibit insulin receptor signaling in pancreatic β-cells. Diabetes 2011;60(4):1198–209. [CrossRef]
21. Rohrbach K, Thomas MA, Glick S, Fung EN, Wang V, Watson L, et al. Ibipinabant attenuates β-cell loss in male Zucker diabetic fatty rats independently of its effects on body weight. Diabetes Obes Metab 2012;14(6):555–64. [CrossRef]
22. Nagappan A, Shin J, Jung MH. Role of Cannabinoid Receptor Type 1 in Insulin Resistance and Its Biological Implications. Int J Mol Sci 2019;20(9):E2109. [CrossRef]
23. Altınok A, Coşkun ZM, Karaoğlu K, Bolkent S, Akkan AG, Ozyazgan S. Δ9-tetrahydrocannabinol treatment improved endothelium-dependent relaxation on streptozotocin/nicotinamide-induced diabetic rat aorta. Acta Physiol Hung 2015;102(1):51–9. [CrossRef]
24. Lavecchia A, Cerchia C. Selective PPARγ modulators for Type 2 diabetes treatment: how far have we come and what does the future hold? Future Med Chem 2018;10(7):703–5. [CrossRef]
25. O'Sullivan SE. Cannabinoids go nuclear: evidence for activation of peroxisome proliferator-activated receptors. Br J Pharmacol 2007;152(5):576–82. [CrossRef]
26. O'Sullivan SE, Kendall DA. Cannabinoid activation of peroxisome proliferator-activated receptors: potential for modulation of inflammatory disease. Immunobiology 2010;215(8):611–6. [CrossRef]