Islet protection and amelioration of diabetes type 2 in *Psammomys obesus* by treatment with cannabidiol[*]

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ABSTRACT

Background and Purpose: Cannabidiol (CBD), a non-psychoactive component of *Cannabis sativa*, has been shown by us, to have an anti-inflammatory effect in collagen-induced arthritis in DBA mice and in type 1 diabetes in NOD mice. As inflammation is a process involved in diabetes type 2, we administered CBD to *Psammomys obesus* (sand rats), a species which develops diabetes type 2 when fed high-energy (HE) diet, to investigate whether we can hinder the development of the disease. Experimental Approach: Male *Psammomys obesus* were kept on a high energy diet during the experiments. They were treated with CBD (i.p injection, 5 mg/kg, 5 times/week) for 4 weeks and kept (without CBD) for another 29 - 39 days. The weights of the animals as well as blood glucose and plasma insulin levels were determined and the morphology of the pancreatic islets was examined. Key Results: CBD significantly reduced blood glucose levels in *Psammomys obesus*, without effecting body weight. Plasma insulin levels were significantly higher in the CBD-treated group. The most striking effect noted was the marked decrease of the destruction of pancreatic islets and beta cells. Conclusions and Implications: CBD partially protects pancreatic islets and beta cells from destruction. CBD lowers significantly the blood glucose level and increases insulin level in *Psammomys obesus* with diabetes type 2, but does not lead to obesity. As CBD already has been administered to patients for other medical indications we propose its use as a therapeutic agent in diabetes type 2.

Keywords: Cannabidiol; Type 2 Diabetes; Islet

Protection; *Psammomys obesus*

1. INTRODUCTION

Obesity and type 2 diabetes (T2D) have reached epidemic proportions in the Western world. T2D is a particularly heterogeneous disorder, despite the many clinical similarities seen in diabetic patients, including hyperglycemia, hypeinsulinemia hyperlipidemia, hypertension and obesity. There is crosstalk between the various tissues involved in the diabetes syndromes: adipose tissue, muscle and liver via signals that include free fatty acids and adipokines. Several investigators have shown significant increased in pro-inflammation cytokines such as IL6, TNF-α and glucose intolerance [1-3].

Cannabidiol (CBD) is a constituent of the *Cannabis sativa* plant, which does not cause psychoactive effects due to its low affinity binding to the CB1 receptor. CBD potential therapeutic activity was documented in several reviews [4-6]. CBD has been shown to posses immuno-modulation [7] and anti-inflammation properties [8,9] It also inhibited the release of the pro-inflammatory cytokines IL-1, TNF-α and IFN-γ by peripheral blood mononuclear cells [10]. We have reported that CBD significantly inhibited insulitis, beta cell destruction and the occurrence of overt type 1 diabetes in NOD female mice [11,12]. We have also found that CBD treatment suppressed the production of the Th1-associated cytokines, IL-12, IFN-γ and TNF-α and enhanced production of the Th2-associated cytokines, IL-4 and IL-10, suggesting a possible gradual progression from destructive Th1 immunity to protective Th2 immunity [11,12].

We previously demonstrated that CBD was effective in suppressing the progression of autoimmune joint destruction in the collagen-induced arthritis animal model of rheumatoid arthritis, a Th1-mediated disease [13]. The anti-autoimmune effects of CBD were associated with reduction in synovial cell TNF-α production, inhibition of reactive oxygen release from zymosan-stimulated

neutrophils and suppression of joint-specific T-cell proliferation and IFN-*γ* production. Although diabetes type 1 differs from diabetes type 2, there are many similar manifestations, such as enhancement of the levels of proinflammation cytokines and free radicals.

We decided to examine the effects of CBD in the *Psammomys obesus*, a model of type 2 diabetes, since CBD inhibits the production of IL-1b, TNF-*α* and IFN-*γ*, cytokines that are involved in the beta cells destruction leading to diabetes. The *Psammomys obesus* in nature feeds on salt bush, which supply most of its nutrients and water. When they are fed a high-energy (HE) diet, they develop diabetes. The Jerusalem colony of *Psammomys obesus* was established from animals from the Dead Sea region. Generally four stages of consecutive progression to diabetes in this species are defined, namely Stage A: Basal normoglycemia and normoinsulinemia. Stage B: Hyperinsulinemia (ranging from 120 to 300 mU/L), while animals remain normoglycemic and gain weight. Stage C: Documentation which entails a marked hyperglycemia together with both hyperinsulinemia and hyperproinsulinemia and further obesity. Stage D: (6 - 12 weeks after stage C) Low plasma insulin, increase of blood glucose, hyperlipidemia, and body weight loss [14].

In this study we examined the effect of CBD on the development of diabetes in male sand rats feeding on high diet, by assaying glucose and insulin levels in blood and analyzing the islets and beta cell integrity in histological sections of the pancreta

2. MATERIAL AND METHODS

2.1. CBD

CBD was extracted from cannabis resin (hashish) as previously reported [15].

For *in vivo* injection, CBD was first dissolved in ethanol and then Cremophor EL (Sigma) was added up to a 1:1 ratio. This solution was further diluted in saline so that the final solution was ethanol/Cremophor/saline (1:1:18).

2.2. *Psammomys obesus*

Psammomys, 4.5 month old, male (Hebrew University Colony, Harlan, Jerusalem, Israel) were fed by a low energy (LE) diet, normoglycemia maintaining diet (2.38 kcal/g; Koffolk, Petach-Tikva, Israel). Diabetes was induced by feeding the animals a high-energy (HE) diet (2.92 kcal/g; cat #2018, Teklad Global Diets, Boston, MA) [14,16]. All experiments were authorized by the Institutional Animal Care Committee.

2.3. Experimental Protocols

In the first experiment, 30 *Psammomys* were divided

into two groups: 15 were treated with CBD and the other 15 with the vehicle (Ctr). To determine the ability of CBD to suppress the diabetic manifestations in *Psammomys*, the animals were injected intraperitoneally (i.p.) with 5 mg/kg CBD, or with the vehicle alone five times/week. The injections continued for 4 weeks, starting 3 days before feeding with the HE diet. Thereafter, the *Psammomys* were kept on High Diet without CBD treatment, for another 29 days (total-60 days from the beginning of CBD treatment). The additional period without treatment was chosen to establish the sustainable effect of the CBD on the beta cells integrity as was found in NOD mice [11,12]. Body weight and tail-blood glucose (Accutrend Sensor; Roche Diagnostics, Mannheim, Germany) were monitored twice a week for one month and once a week thereafter.

Twenty nine days after the end of CBD treatment, the animals were anesthetized with Ketalar (Parke-Davis, Gwent, UK) and the blood was collected in 10% EDTA, by cardiac puncture. The pancreata were fixed in 10% formalin in buffer, for histological analysis. Serum was stored at −20˚C for analysis of insulin.

In the second experiment, 20 animals were used, 10 animals for the vehicle-treated and 10 for the CBD-treated group (5 mg/kg CBD, five times/week, for 4 weeks). The animals were monitored as in the first experiment. The experiment was ended, 39 days after the end of CBD treatment, total of 70 days, from the beginning of CBD treatment.

2.4. Histology

Pancreatic tissue was fixed in 10% buffered formalin and was embedded in paraffin. The 5-micron sections were stained with hematoxylin and eosin. Sections were screened and scored by two independent observers.

2.5. Statistical Analysis

Data were expressed, as means ± SEM. Statistical analysis was carried on, as specified in the results.

P value was considered significant when $P \leq 0.05$.

3. RESULTS

3.1. Weight of CBD-Treated Psammomys

The weights of the CBD-treated *Psammomys*, in the two experiments, were not significantly different between the treated and control animals, as determined by the Fisher Exact Test (see **Figures 1(a)**, **(b)**).

3.2. Glucose Levels of CBD-Treated *Psammomys*

It has been observed previously that *Psammomys* be-
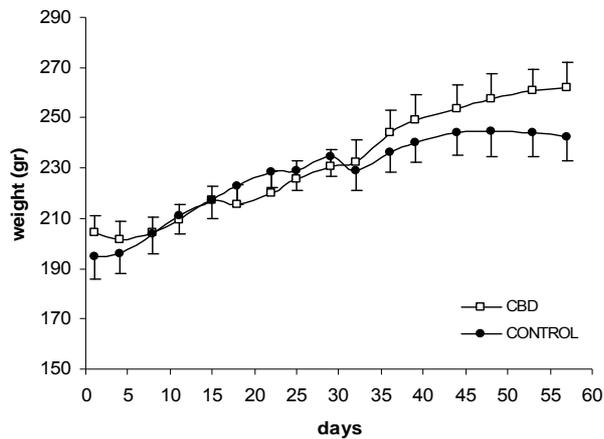
(a)
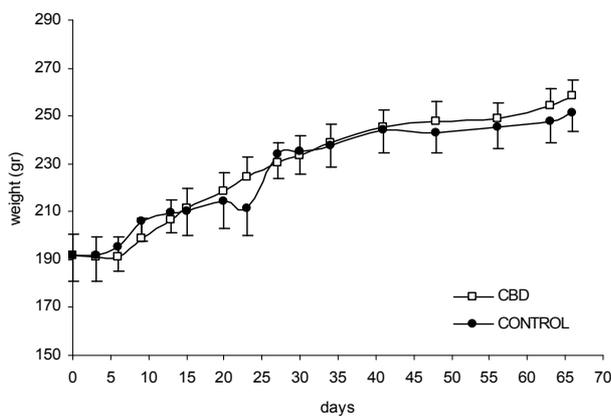
(b)

Figure 1. Weight of the *Psammomys* following CBD treatment. (a) Experiment 1, observation for 60 days; (b) Experiment 2, observation for 70 days. CBD was injected ip 5 mg/kg (5 times/week) from day 3 to day 31. Controls were injected with the vehicle: Non significant-treated vs. control p > 0.05.

come diabetics (glucose >200 mg/dl) when they are transferred to HE diet. Within 7 days—81% of the animals reach blood glucose level over 200 mg/dl and over 90% of them—within 14 days [16].

In our first experiment (60 days observation) 13 rats (86%), out of 15 control *Psammomys*, developed diabetes (glucose > 200 mg/dl) within 30 days (**Figure 2(a)**).

In contrast, only 4 animals (25%), out of 15, in the CBD-treated group (5 mg/kg, 5 times/week) developed hyperglycemia (over 200 mg/dl). The CBD-treated *Psammomys* had significantly lower mean glucose levels compared to the vehicle-treated *Psammomys* (P ≤ 0.05) (**Figure 2**).

In the second experiment (70 days observation, **Figure 2(b)**), in the control group, 6 out of the total 7 (86%) *Psammomys* developed diabetes (3 died). Whereas only 4 of 10 (40%) of the CBD-treated *Psammomys* had hyperglycemia and all these animals survived (**Figures 2(a)**, **(b)**).
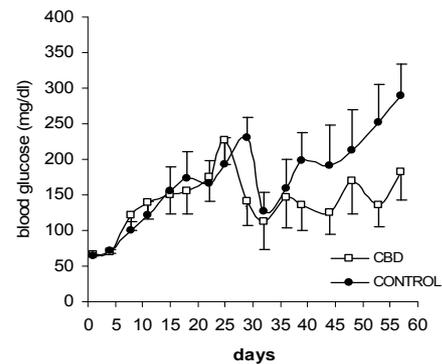
(a)
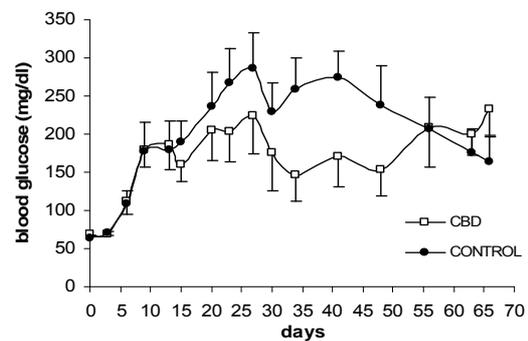
(b)

Figure 2. Levels of blood glucose in plasma of *Psammomys* following CBD treatment. (a) Exp. 1; (b) Exp. 2. See details in **Figure 1**. Non-significant-Treated vs. Control P ≤ 0.05.

Least-squares linear regression was used to fit the level of glucose as a function of time, separately for each animal. The regression coefficients (slopes) were then employed in Mann-Whitney test on the combined sample. The CBD lowered the rate of a glucose increase significantly (P ≤ 0.05) as determined by a Mann-Whitney test on the combined sample).

3.3. CBD Prevents Insulin Depletion in Diabetes-Prone *Psammomys*

The most prominent characteristic of diabetic *Psammomys* is the rapid depletion of pancreatic insulin stores [17] which probably result from prolonged *β*-cell stimulation by the HE diet. This mechanism plays an important role in the development and progression of diabetes in the *Psammomys* model. In the present study in both experiments the plasma levels of insulin in the vehicle-treated control (median at 118 - 142 μU/ml) were significantly lower than the CBD-treated groups (153 - 210 μU/ml) (**Figure 3**) Also the CBD-treated animals, tended to maintain their insulin at the pre-HE levels, probably as a result of cyto-protection conferred to the pancreatic *β*-cells by CBD.

(a)

(b)
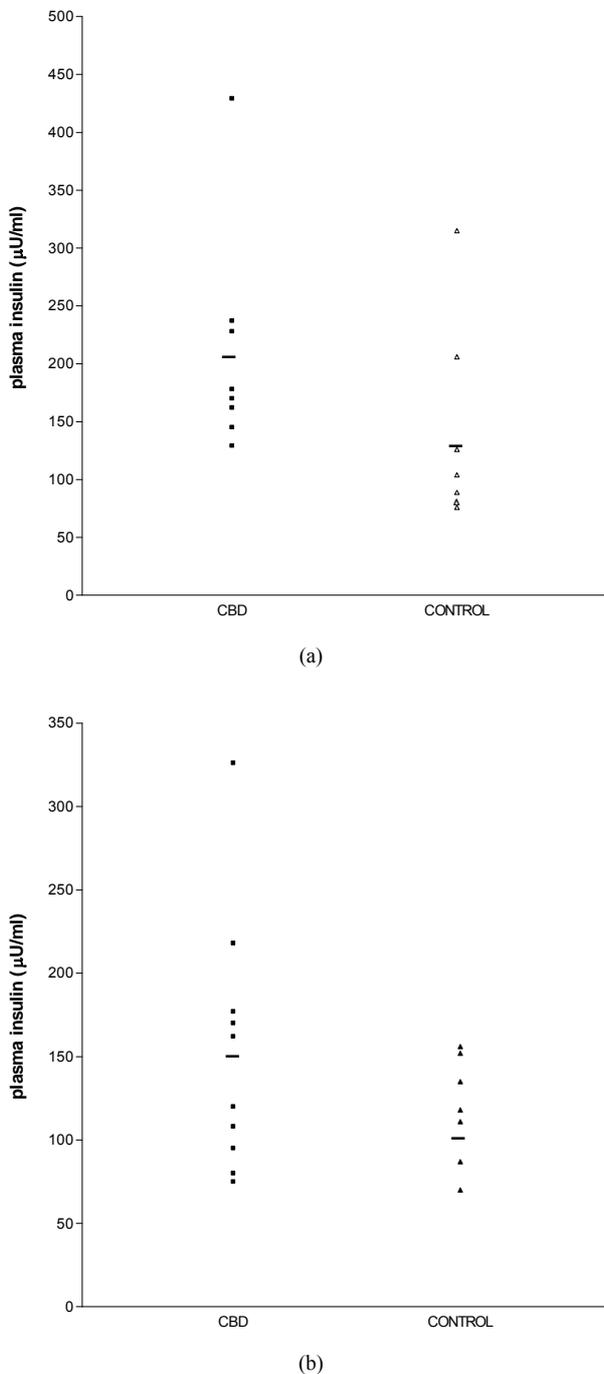
Figure 3. Insulin levels (μU/ml) in *Psammomys* plasma at the end of the CBD treatment experiments. (a) Exp.1, mean insulin in CBD-treated group was 209.8 μU/ml, in the control 142 μU/ml (non significant); (b) Exp.2, mean insulin in CBD-treated group was 153 μU/ml, in the control group 118 μU/ml Significant-treated vs. control P ≤ 0.05.

In order to increase the statistical power, the data from the two experiments were combined. A Mann-Whitney test was then used to compare insulin levels in the experimental animals with those in the controls.

3.4. Animal Survival

CBD-treatment increased, although not significantly, the *Psammomys* survival as seen in **Table 1**. In the two experiments, 13/25 (52%) of the controls survived, whereas in the CBD-treated animals, 18/25 (72%) survived at the end of the two experiments.

There is no statistical difference in survival between the treated and untreated animals (P = 0.20, as determined by the Fisher Exact Test).

3.5. CBD Protects *β*-Cells from Destruction

The morphological evaluation of the pancreata histological sections of the control group showed abnormal islet morphology. About 20% of the islets were without regular borders and were destroyed, also a high percentage of the islets (75%) were with many vacuoles (**Table 2** and **Figures 4(b)**, **(c)**).

On the other hand, in CBD- treated animals, no damaged islets were observed and most of them were normal. Also, only 26% of the islets had numerous vacuoles. The quantitative morphological results of Langerhans islets are given in **Table 2** and the morphology of the islets is demonstrated in **Figure 4**. The control islets (**Figures 4(b)**, **(c)**), show giant cells with vacuoles as well as destroyed islets, with no islet border and only few beta intact cells, whereas the islets from the CBD-treated animals, were normal (**Figure 4(a)**). Thus, the histological assessment is in line with the results of blood glucose and plasma insulin levels. These findings demonstrate that the treatment with CBD protects the pancreatic *β*-cells integrity against the excessive release of insulin into

Table 1. *Psammomys* survival following CBD treatment.

Experiment	Survival			
	after 30 days		**after 57 - 66 days**	
	Control	CBD	Control	CBD
Exp. 1	7/15	11/15	7/15	8/15
Exp. 2	7/10	10/10	6/10	10/ 10
Exp. 1 and Exp. 2	14/25	21/25	13/25	18/25
% survival	56	84	52	72

Table 2. Morphological study of *Psammomys* langerhans islets[*].

Morphology	CBD Treatment	Control
Normal + very few small vacuales	79 (62%)	30 (38%)
Many Vacuoles	51 (26%)	147 (74%)
Damaged Islets	0 (0%)	19 (100%)

[*]Data of 2 experiments.
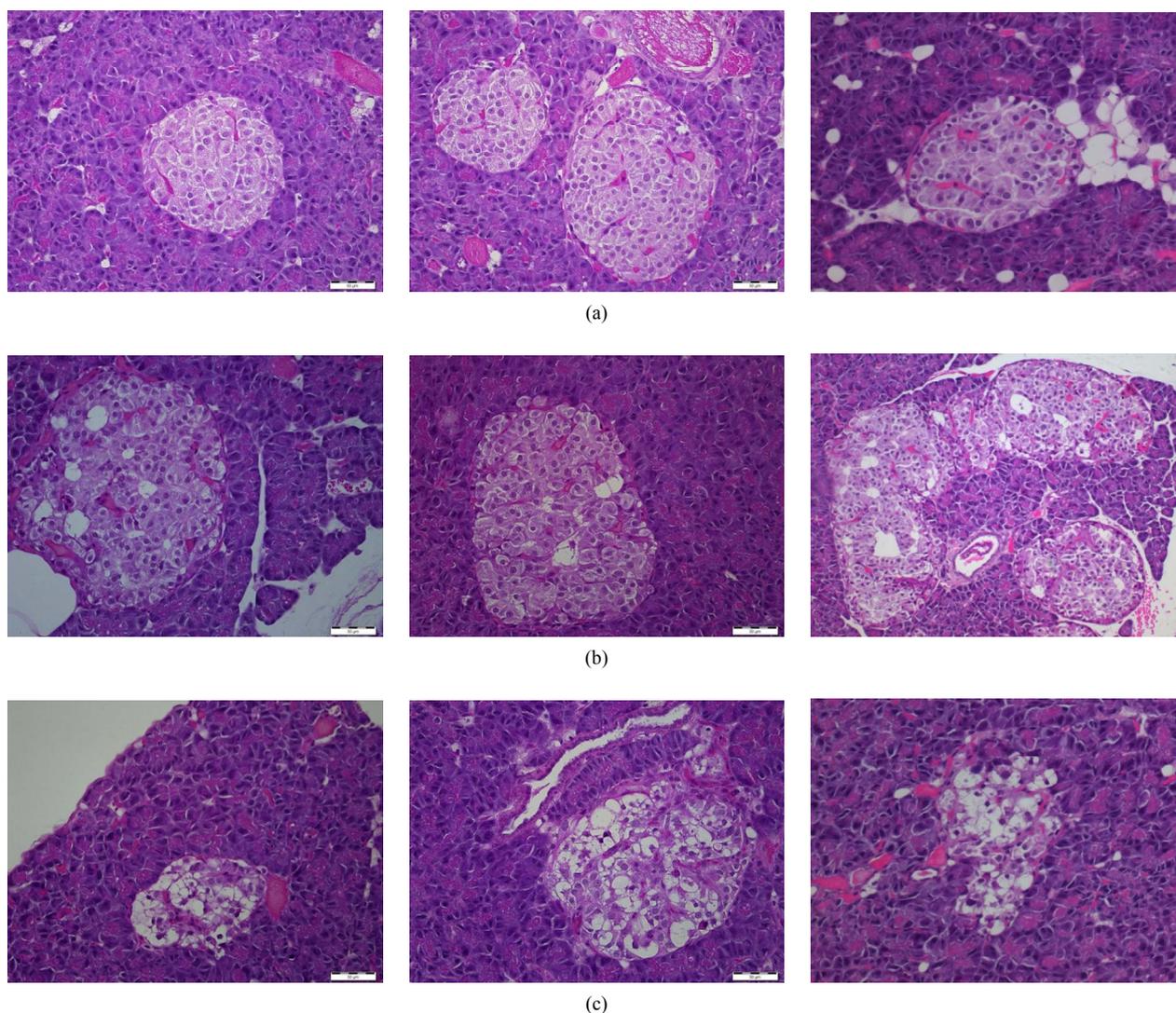
Figure 4. Photomicrographs of Langerhans islets of *Psammomys obesus*. (a) Normal Islets of CBD-treated *Psammomy*; (b) Giant Islets with vacuoles from vehicle-treated *Psammomys* (control); (c) Damaged/destroyed islets from vehicle-treated *Psammomys* (control).

the blood and preserves the islet's normal morphology.

4. DISCUSSIONS

In this study we show that CBD treatment prevents the damage to the islet structure, preserves islet insulin content and prevents the destruction of beta cells which is induced by the HE diet.

We demonstrate that four weeks of CBD treatment (5 mg/kg) is effective in preserving normoglycaemia in the majority of the *Psammomys* keeping on a HE diet, whereas the vehicle-treated animals became hyperglycemic.

The *Psammomys obesus* exhibits normally insulin resistance in its native environment, which is seen both in muscle and liver [18]. On transfer to HE diet they develop nutrition-dependent diabetes with a clinical and immunological course very similar to human type 2 diabetes. Diabetes in the *Psammomys* is characterized by hyperglycemia, hyperinsulinemia followed by depleted pancreatic insulin. Normoglycemic diabetes-prone *Psammomys obesus* which were fed HE diet, developed hyperglycemia within 4 - 14 days, together with a progressive decline of pancreatic insulin content, increased rate of beta-cell death and damage to the islets. Indeed, exposure of islets from diabetes-prone *Psammomys obesus* to high glucose levels, *in vitro*, results in increase in apoptosis of beta-cells [17,19].

Generation of reactive oxygen species may represent an alternative mechanism for both glucotoxicity and lipotoxicity. Hence CBD, a non-psychoactive component of marijuana, which possesses antioxidant, anti-inflammatory and immunosuppressive properties can be ex-

pected to have positive effects. Indeed, Patane *et al.* [20] showed that treatment of islets with metformin, which also has antioxidant properties, protects the islets from the harmful effect of free fatty acids and restores the insulin secretion after chronic exposure to free fatty acids or high glucose. In our study we demonstrate the ability of CBD to significantly reduce the incident of diabetes in male *Psammomys* and to protect the pancreas islets from destruction. Our previous results [11,12] indicate that CBD can decrease both the incidence of autoimmune type 1 diabetes, as well as the destruction of the islets in NOD female mice.

It has been argued that inflammation is involved in the pathogenesis of diabetes type 2 [21,22]. As in all inflammatory Th1-associated diseases, the reduction of proinflammatory cytokine production, with an increase in IL-4 and IL-10, as demonstrated in the NOD mice, suggests that a mechanism of immunomodulation is involved, namely an immune shift from Th1 to Th2. Another mechanism that might be involved in our study is based on the anti-oxidative activity of CBD [13,23], that very likely prevents beta cell destruction in the HE fed *Psammomys*. Vanadyl sulfate and rosiglitazone have also been found to be effective in preventing hyperglycemia and hyperinsulinemia [24,25], while nicotine treatment [26] caused decrease in food intake and body weight. An antidiabetic effect was also obtained by G protein kinase analogs [27] and electroacupuncture [28].

CBD administration did not cause obesity in *Psammomys*, therefore, it may be assumed that CBD does not enhance muscle or liver insulin sensitivity or improve lipid metabolism in this species.

It is known that HE diet which induces glucotoxicity, causes damage to *Psammomys* beta cells. Several studies [29,30] have reported changes of islets morphology of *Psammomys* maintained on a HE diet, namely a gradual destruction of beta-cell, loss of insulin, apoptosis and necrosis. Our study clearly demonstrates that CBD has a beneficial effect on the integrity of *Psammomys* pancreatic islets. It was reported [31] that CBD attenuated high glucose-induced endothelial cell inflammatory response by inhibiting NF-kb nuclear translocation.

Irreversibility of nutritionally induced type 2 diabetes in *Psammomys* is related to beta cell apoptosis [17,32,33] although this aspect was not explored in our study.

The significant increased insulin availability in CBD treated animals counteracts insulin resistance, which is essential for reducing glucose concentrations in the plasma during HE diet and for preservation of pancreatic beta cell function.

One can assume that the normoglycemia in *Psammomys* will be associated with normal level of serum insulin concentrations; however CBD treatment did not reduce, but rather increased these concentrations. Also the hy-

perinsulinemia fallowing CBD administration did not cause obesity. We can assume that CBD does not change insulin sensitivity in *Psammomys*.

The cytokines level could not be assayed in our experiments, due to lack of available cytokines tests for *Psammomys*. However, one can speculate that the reduction of inflammatory cytokines following CBD treatment in mice [11,12] might also play a role in the outcome of CBD treatment in *Psammomys*.

Plasma TNF-α is associated with insulin resistance. This supports the claim that TNF-α plays a significant role in the pathogenesis of chronic insulin resistance in humans [34] It has been shown that visfatin, TNF-α, and IL-6 mRNA expressions are increased in peripheral mononuclear-monocytic cells from women with type 2 diabetes, independent of their BMI [35].

Since CBD is known to inhibit production of IL-1b, TNF-α and IFN-γ in mice [11,12] and that these factors are known to be involved in the pathway of autoimmune islet cell destruction leading to diabetes, it may represent one of the mechanisms involved in the lack of islets destruction and preservation of normal glucose levels in the plasma.

Several mechanisms of action of CBD were proposed [4], among them FAAH inhibition, adenosine uptake inhibition and PPAR gamma activation as well as attenuation of oxidative/nitrosative stress. Moreover, CBD has been applied in various clinical conditions to human patients [5] without any observed toxic effects.

As CBD already has been administered to patients for other medical indications [4,6] and proved to be extremely safe, we propose its use as a therapeutic agent in diabetes type 2.

5. ACKNOWLEDGEMENTS

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