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Short communication

Analysis of hypoglycemic effects of cannabidiol following oral and intraperitoneal administration in healthy rats

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Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder with multifactorial complex etiology. It is characterized by a failure of glucose homeostasis and disturbances of carbohydrate, protein and lipid metabolism, attributed to defects in insulin secretion and/or insulin effect. Standard antidiabetic therapy comprises exogenous insulin and/or various oral antidiabetic medications, which are contraindicated in certain subpopulations of patients and frequently associated with serious adverse effects (Jadoon et al., 2016). Therefore, prompt research for novel hypoglycemic agents is urgently required.

The most abundant non-psychotropic cannabinoid from *Cannabis sativa* is cannabidiol (CBD), which gained increased attention regarding its extensive spectrum of biological activities and favorable safety profile (Lim et al., 2021). Previously conducted studies disclosed that CBD administration is related to great therapeutic potential for treatment of streptozotocin (STZ)-induced DM, mostly affecting the oxidative stress, inflammation, and cell death (Jadoon et al., 2016). However, there are some discrepancies in the literature concerning whether or not CBD has a direct effect on blood glucose levels, both, in animal models (Frisher et al., 2010) and in humans (Jadoon et al., 2016; Mattes et al., 2021). These inconsistencies are likely due to the different doses and administration routes of CBD used in distinctive studies.

Thus, the objective of this study was to investigate the potential hypoglycemic effects of different doses of CBD in healthy rats. Moreover, we aimed to compare the effectiveness of the same doses of CBD given both orally and via intraperitoneal route of administration in rats. Finally, further investigations will be made in diabetic rats, for estimation of the potential antihyperglycemic effects of CBD oil.

Materials and methods

CBD oil preparation

CBD extract was obtained by CO_2 extraction of Cannabis flos (decarboxylated), diluted with olive oil to 25% (w/w).

Animals and treatment

Healthy female Wistar rats (weighted 250±10 g, aged 14-16 weeks) obtained from the Vivarium of the Faculty of Natural Sciences and Mathematics, Skopje were used. The animals were kept under standard environmental conditions (12-h light and 12-h dark cycle; 20 ± 2°C), fed with standard rat pellet diet and provided water *ad libitum*. The animals were divided into 8 groups (n=4): control group, metformin-receiving group (75 mg/kg body weight), three groups receiving different CBD doses via oral route (0.5, 5 or 50 mg/kg body weight) and three groups receiving different CBD doses via intraperitoneal route (0.5, 5 or 50 mg/kg body weight).

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Oral glucose tolerance test (OGTT)

After an overnight fast (8h), basal glycaemia was measured from the tail vein using a glucose oxidase-peroxidase reactive strips (and a glucometer (Plusmed, Istanbul, Turkey). Water as a control, metformin or CBD oil in previously defined doses and administration routes were given to each animal according to which group it was randomized. Thirty minutes later, animals received glucose solution (2 g/kg), using a gavage. Blood samples were collected immediately after glucose administration and then after 15, 30, 45, 60, 90 and 120 min. respectively, in order to obtain the glycemic area under the curve (AUC).

Statistical analysis

Statistical analysis was performed by one-way analysis of variance (AN OVA) followed by Tukey's *post hoc* test. The results were considered statistically significant at $p \leq 0.05$. GraphPad Prism (ver. 9) software was used for statistical analysis.

Results and discussion

The results obtained from the OGTT showed that all three groups that were given CBD intraperitoneally, as well as the metformin-receiving group, have overall similar dynamics towards blood glucose levels during the 120 minute time period. Namely, glucose levels in aforementioned groups peaked at similar levels 15 minutes after glucose administration, declined after 30 minutes, and reached values observed in the control group after 60 minutes. However, there was no significant difference in the overall response between the different doses of CBD regarding the AUC.

Throughout the OGTT measurements in the CBD-receiving groups via oral route, glucose levels in all three groups peaked at similar levels 15 minutes after the glucose administration. It is noteworthy that the group treated with 50 mg/kg CBD showed a significantly lower increase in glucose levels over the first 15 min after glucose administration, compared to the control and metformin-treated groups. Similarly to the metformin-treated group, the CBD-treated groups with doses of 0.5 mg/kg and 50 mg/kg reached the values obtained in the control group 60 minutes after glucose administration, while the rats treated with 5 mg/kg CBD reached control values after 90 minutes. Furthermore, the glycemic AUC value for the treatment with 50 mg/kg CBD was approximately 10% lower than the AUC value for the metformin-treated group ($p \leq 0.05$). In addition, when compared with the rats treated with 0.5 mg/kg and 5 mg/kg CBD, the AUC values were lower by 10% and 15% lower respectively. Moreover, orally given CBD at the dose of 50 mg/kg had the best overall glucose response.

Conclusion

In conclusion, we have demonstrated that oral and intraperitoneal application of CBD generates hypoglycemic effects in healthy rats subjected to OGTT. Moreover, the dose of 50 mg/kg, administered via oral route, was more effective than the standard hypoglycemic agent metformin. These findings raise the possibility that potential mechanisms underlying these effects could have novel application in therapeutics for diabetes.

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