IT IS NOT ENDOCANNABINOIDS BUT THE TYPE AND AMOUNT OF FOOD ARE THE MAIN CAUSE OF METABOLIC DISTURBANCES IN RATS


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Abstract: Obesity has been identified as a major global health problem. A major cause of the obesity is the changes in feeding behaviour. Many controversy data concerning the role of endocannabinoid system in regulation or disturbing of the metabolic parameters. The aim of this research is to identify the effect of methanandamide (as a one of CB1 selective agonist) on some metabolic parameters in rats fed by different types of food to clarify which is the cause of metabolic abnormality in obese.

Design: A total number of 56 healthy adult male albino rats were used to study the effect of different types of diet and daily i.p injection methanandamide (CB1 agonist) in a dose of 0.5 mg/kg BW for 6 weeks on some metabolic parameters using pair feeding paradigm. Results: a significant increase in final body weights and a significant dyslipidemia and hyperglycemia with insulin resistance was in both HFD and HFrD fed groups when compared with that of standard chow diet fed group. Moreover, a significant dyslipidemia and hyperglycemia with insulin resistance was observed in methanandamide treated ad libitum group. In addition, our study revealed an insignificant change in all parameters measured between HFD and HFrD fed groups except for TG and VLDL parameters which are significantly higher in HFrD-fed group in comparison with that of HFD fed group.

Interestingly, an insignificant change in serum levels of all previously mention parameters in the three different methanandamide treated pair fed groups in comparison with that of the three different fed control groups respectively.

Conclusion: we can conclude that endocannabinoid system is not the main responsible for metabolic disturbance in obese rats.


Key Words: high fat, high fructose, endocannabinoid, insulin resistance, dyslipidemia.

1. Introduction:

The history of marijuana and its medicinal use go back thousands of years, but the endogenous counterparts of cannabis, the endocannabinoid (ECs) have only been known about 18 years ago, their discovery have been triggered by the identification of specific cannabinoid receptors in the brain. Two subtypes of cannabinoid (CB) receptors have been identified to date. Both CB1 and CB2 receptors couple to the Gi/o subtypes of G proteins, but can also activate additional, G protein-independent pathways.

It is common knowledge that marijuana use improves appetite, presaging the role of ECs as endogenous orexigenic factors. However, findings as early as the 1970’s suggested that Δ9-tetrahydrocannabinol (Δ9THC), the psychoactive ingredient of marijuana, has additional metabolic effects unrelated to appetite.

CB1 receptors are present in skeletal myocytes and are upregulated in obesity and may be one of the targets for cannabinoid-induced insulin resistance. ECs may also influence insulin secretion in the endocrine pancreas, although there are conflicting reports on CB1 receptors mediating a decrease or an increase in insulin release, so ECs may share in the regulation of glucose homeostasis and insulin sensitivity.

Metabolic studies have confirmed that calories obtained from fat have a greater role in obesity and have been considered as dietary risk factors for metabolic syndrome (MS), moreover, fructose as a common supplement of the packed food has been implicated as a possible cause of the MS.

CB1 receptor inhibition by AM251 is capable of countering insulin resistance in adipose tissue, muscle and liver. However, similar beneficial effects on insulin sensitivity were also observed in pair fed animals. The lack of significant improvement in metabolic status in AM251 treated, in comparison to pair fed animals does not mirror this finding. Thus, further studies are necessary to confirm these initial observations. Interestingly, AM251 also increased locomotor activity in agouti mice.

Recently, Sink et al. reported that all clinically available cannabinoid receptor antagonists (e.g. AM 251 and rimonabant “SR141716A”) are inverse agonists that can target CB1 receptors located in both central circuits regulating appetite and motivation and in peripheral organs regulating metabolism and energy expenditure. This profile (inverse agonism)
complicates understanding of cannabinoid CB1 receptor blockade as a therapeutic strategy in obesity and metabolic disorders.

Unlike rimonabant, chronic administration of LH-21 (selective CB1 antagonist only) reduces feeding but does not improve hypertriglyceridaemia or hypercholesterolaemia; nor does it reduce liver fat deposits in Zucker rats. These data explain why AM251 increased locomotor activity in agouti mice at low doses\cite{13}.

It is still uncertain whether an overactive ECS is an early cause\cite{15} or just one of the several consequences, of HFD and the subsequent development of overweight and obesity.

The present study was done to identify the effect of methanandamide (as a one of CB1 selective agonist) on some energy metabolic parameters concerning glucose homeostasis and lipid in rats fed by different types of food (commercial, high fat and high fructose diet) using pair feeding paradigm in a trial to clarify which is the cause of metabolic abnormality in obese, it is ECS alone, type of food, amount of food intake or crosstalk between them?.

Materials And Methods

Animals

This study was carried out on a total number of 56 adult (4 months; body weight, 180-200 gm) healthy male albino rats. Under hygienic conditions, in the animal house of the faculty of medicine Zagazig University, all rats had free access to water and chow, supplied in separate clean containers. Rats were kept at comfortable temperature (20 to 24 °C) and were maintained on a 12 hr light/dark cycle\cite{16}.

Diet

Normal (standard) diet: consists of commercial rat standard chow [it was consisted of 25.8 % protein, 62.8 % carbohydrate and 11.4 % fat\cite{20}].

High fat diet (HFD): was consisted of 16.4% protein, 25.6% carbohydrate, and 58.0% fat (a total 23.4 kJ/g) in the form of cotton seed oil added to the laboratory chow diet\cite{17,18}.

High fructose diet (HFrD): commercial rat laboratory chow containing 60% fructose\cite{19}.

Methods

The rats were accommodated to the new laboratory conditions for three weeks before the beginning of the experimental regimen\cite{21}. Grouping of the animals

Group I "normal fed group": to study the effect of 6 weeks normal diet. It is consists of 24 rats which further subdivided into 3 equal subgroups (n= 8):

Group IA: vehicle (saline) treated group with access to ad libitum standard chow.

Group IB: Methanandamide (dissolved in sterile saline), treated (0.5 mg/kg BW i.p, daily)\cite{21,22}, pair fed group. Rats were given a weighed amount of standard chow each day corresponding to the amount consumed by vehicle treated rats on the previous day\cite{22}.

Group IC: Methanandamide treated (0.5 mg/kg BW i.p, daily), ad libitum group, rats had access to ad libitum standard chow.

Group II "HFD fed group": to study the effect of 6 weeks HFD diet. It consists of 16 rats which further subdivided into 2 equal subgroups (n= 8):

Group II A: vehicle treated group with Access to ad libitum HFD.

Group II B: Methanandamide treated (0.5 mg/kg BW i.p daily), HFD pair fed group.

Group III "HFrD fed group": to study the effect of 6 weeks HFrD diet. It consists of 16 rats which further subdivided into 2 equal subgroups (n= 8):

Group III A: vehicle treated group with Access to ad libitum High fructose diet.

Group III B: Methanandamide treated (0.5 mg/kg BW i.p, daily), HFrD pair fed group.

For all groups, body weight was recorded at the beginning and the end of the study period (6 weeks).

Sampling of blood

At the end of the experimental period (at the end of 6th week) after overnight fasting, at 8:00 a.m, blood samples were obtained from sinus orbitus vein of each rat after ether inhalation\cite{23}. The blood samples were allowed to clot at room temperature before centrifuging at approximately 3000 rpm for 15 minutes. The serum was stored at -20 °C.

Serum analysis

Determination of serum glucose level: According to Trinder\cite{24} using glucose enzymatic (GOD-PAP)-liquizyme Kits (Biotechnology, Egypt).

Determination of serum insulin level: By a solid phase enzyme amplified sensitivity immunoassay according to Starr et al. \cite{25} using KAP1251-INS-EASIA (Enzyme Amplified Sensitivity Immunoassay) Kits (BioSource Europe S.A., Belgium).

Determination of the Serum total cholesterol (TC): by enzymatic colorimetric method according to Allain\cite{26} using Cholesterol RTU 61218 kits: (bioMerieux S.A., Lyon, France).

Determination of the Serum high density lipoprotein cholesterol (HDL): by enzymatic colorimetric method according to Warnick et al.\cite{27}, using Stanbio HDL-cholesterol procedure No. 0599.
Determination of the Serum Triglyceride levels: It was carried out according to Naito[28] using triglycerides ESPAS SL kits (Elittech S.A., Sees, France.).

Calculation of very low density lipoprotein cholesterol (VLDL) and Low density lipoprotein cholesterol: According to Friedewald et al. [29].

HOMA-IR was assessed by homeostasis model assessment (where HOMA= fasting serum insulin (µIU/mL) x [fasting serum glucose (mmol/L)/22.5])[30].

The data obtained in the present study were expressed as mean ± SE for quantitative variables and statistically analyzed by using SPSS program (version 18 for windows) (SPSS Inc. Chicago, IL, USA). P value <0.05 was considered statistically significant.

3. Results:

Table 1& 2 and histograms 1, 2, 3, 4, 5, 6, 7, 8 & 9 show the final body weight (gm), serum glucose (mg/dl), insulin (µIU/mL), the HOMA index of insulin resistance (HOMA-IR), total cholesterol (CHO) (mg/dl), HDL-C(mg/dl), triglyceride (TG) (mg/dl), VLDL (mg/dl) and LDL-C(mg/dl) levels in all studied groups. In group IB “Methanandamide treated normal diet pair fed group” the mean values were found to be non significant (P > 0.05) when compared with that of group 1A “normal diet control group”, however group IC “Methanandamide treated normal diet ad libitum” were found to be significantly higher than that of both group 1A and group IB (P < 0.01, P < 0.001, P < 0.001, P < 0.001, P < 0.001, P < 0.001, P < 0.001 & P < 0.001 respectively) except HDL-C levels was significantly lower. In addition, the mean values of group IIB “Methanandamide treated HFD pair fed group” and III B “Methanandamide treated HFrD pair fed group” were found to be non significant (P > 0.05) when compared with that of group IIA “HFD control group” and IIIA “HFrD control group”.

It was found that both of group IIA “HFD” and group IIIA “HFrD” showed a significant increase in final body weights, serum glucose, insulin, the HOMA-IR, CHO, TG, VLDL-C, LDL-C levels (P <0.001) and HDL-CHO (P < 0.01 & P < 0.05) when compared with that of group IA normal diet group”. While, group IIIA “HFrD” showed an insignificant change (P > 0.05) in final body weights, serum glucose, insulin, the HOMA-IR, CHO, and LDL-C levels, however, it had significant increase in TG and VLDL (mg/dl) (P < 0.001) when compared with that of group IIA “HFD”.

In addition, there were significant positive correlations between final body weights and serum glucose, serum CHO, serum TG, serum VLDL-C, serum VLDL-C, LDL-C levels and calculated HOMA-IR, accompanied by significant negative correlation between serum HDL-C levels and final body weights in all studied groups.

### Table 1: Final body weights, serum glucose, insulin, the HOMA-IR, levels in all studied groups.

<table>
<thead>
<tr>
<th>parameter</th>
<th>N=8</th>
<th>Normal Diet</th>
<th>Group IA</th>
<th>Group IB</th>
<th>Group IC</th>
<th>Group IIA</th>
<th>Group IIB</th>
<th>Group IIIA</th>
<th>Group IIIB</th>
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<tbody>
<tr>
<td><strong>Final body weight (gm)</strong></td>
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<td></td>
<td></td>
<td>241.25±2.13</td>
<td>243.63±2.93</td>
<td>255.25±3.47</td>
<td>266.86±3.47</td>
<td>267.25±3.06</td>
<td>264.50±2.49</td>
<td>264.87±2.81</td>
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<tr>
<td>P</td>
<td></td>
<td>NS</td>
<td>&lt;0.01**</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td><strong>Glucose (gm/dl)</strong></td>
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<td></td>
<td></td>
<td>89.63±6.0</td>
<td>93.13±7.75</td>
<td>219.63±3.64</td>
<td>272.0±6.67</td>
<td>273.5±5.5</td>
<td>281.75±4.41</td>
<td>280.75±4.89</td>
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<tr>
<td>r</td>
<td></td>
<td>+.752</td>
<td>+.795</td>
<td>+.771</td>
<td>+.890</td>
<td>+.948</td>
<td>+.866</td>
<td>+.881</td>
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<tr>
<td>P</td>
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<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
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<td><strong>Insulin (µIU/mL)</strong></td>
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<td></td>
<td></td>
<td>21.04±0.93</td>
<td>21.05±0.69</td>
<td>36.44±1.78</td>
<td>40.25±1.61</td>
<td>39.17±1.21</td>
<td>38.68±1.18</td>
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<tr>
<td>r</td>
<td></td>
<td>+0.749</td>
<td>+0.804</td>
<td>+0.920</td>
<td>+0.932</td>
<td>+0.977</td>
<td>+0.775</td>
<td>+0.932</td>
<td></td>
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<tr>
<td>P</td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
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<td>&lt;0.01</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
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<tr>
<td><strong>HOMA index</strong></td>
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<td></td>
<td></td>
<td>4.69±0.44</td>
<td>4.88±0.49</td>
<td>20.12±1.26</td>
<td>27.57±1.71</td>
<td>26.93±1.34</td>
<td>27.35±1.22</td>
<td>28.00±1.19</td>
<td></td>
</tr>
<tr>
<td>r</td>
<td></td>
<td>+0.901</td>
<td>+0.921</td>
<td>+0.920</td>
<td>+0.937</td>
<td>+0.981</td>
<td>+0.832</td>
<td>+0.848</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
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</table>

* VS group IA
$ VS group IB
Table 2: Serum CHO, TG, VLDL-C LDL-C levels in all studied groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Diet</th>
<th>HFD</th>
<th>H Fr. D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group IA</td>
<td>Group IB</td>
<td>Group IC</td>
</tr>
<tr>
<td>CHO</td>
<td>106.0±2.66</td>
<td>101.50±2.24</td>
<td>133.88±5.30</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>NS</td>
<td>&lt;0.001$</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>NS</td>
<td>&lt;0.001$</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>r</td>
<td>P</td>
<td>NS</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>51.0±1.65</td>
<td>47.75±3.08</td>
<td>38.63±1.55</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>NS</td>
<td>&lt;0.001$</td>
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<tr>
<td>VLDL-C (mg/dl)</td>
<td>NS</td>
<td>&lt;0.001$</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>r</td>
<td>P</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-CHO (mg/dl)</td>
<td>NS</td>
<td>&lt;0.001$</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>r</td>
<td>P</td>
<td>NS</td>
</tr>
</tbody>
</table>

* VS group IA  $ VS group IB

![Histogram 1: The final body weights (gm) in all studied groups. *VS group IA $ VS group IB](Image)

![Histogram 2: illustrates serum glucose levels (mg/dl) in all studied groups. *VS group IA $ VS group IB](Image)

![Histogram 3: illustrates serum insulin levels (µU/ml) in all studied groups. *VS group IA $ VS group IB](Image)

![Histogram 4: illustrates HOMA index of insulin resistance in all studied groups. *VS group IA $ VS group IB](Image)
4. Discussion:

In mammals, body weight and composition are maintained within a narrow range by the integrated control of energy intake, storage and expenditure. The endocannabinoid system (ECs) which consists of cannabinoid receptors, the endogenous lipid ligands (endocannabinoids), and the machinery for their biosynthesis and metabolism share in this control[31].

To explore the exact role of diet and ECs in metabolic disturbance, the present study used the 6 weeks pair-feeding paradigm to ascertain if the metabolic effect of ECs were related to type and/or amount of food intake or not.

As regard HFD ad libitum group, it showed a significant increase in final body weight with preservation of its correlation with all metabolic parameters, and a significant disturbance in glucose metabolism, distinguished by significant increase in fasting serum glucose levels, fasting serum insulin levels, and HOMA index of insulin resistance. Ad libitum HFD fed group also showed dyslipidemia proved by significant increase in serum total cholesterol, TG, VLDL-cholesterol levels, and LDL-cholesterol levels, accompanied by a significant decrease in HDL-cholesterol levels when compared with that of ad libitum normal diet group.

These data are in consistent with Alsaif and Duwaihy[32] who found that in general, HFD significantly increased weight gain, impaired glucose tolerance and increased insulin resistance.

Buettner et al.[33] stated that long term HFD feeding often impairs lipid metabolism by reducing insulin sensitivity of peripheral tissue.

HFD decrease insulin-stimulated glucose disposal in skeletal muscle and increase TG, long-chain acyl-CoA and diacylglycerol contents[34]. In addition, Glut 4 mRNA in WAT is down-regulated by HFD[35].
The HFD induced glucose intolerance and dyslipidemia which proved in the present study can be explained by disturbance of some metabolic hormones such as insulin resistance which has been proved in our results. In addition, Naitoh et al.\cite{36} confirmed that mRNA expression level of adiponectin in WAT and plasma adiponectin levels were found to be decreased in HFD-fed mice compared with commercial diet-fed mice. This hypoadiponectinemia was closely linked to insulin resistance and low HDL cholesterol\cite{37}, as adiponectin enhance lipid clearance from plasma and increasing fatty acid beta oxidation in muscle\cite{38}.

It was found that, diet induced obesity in humans and rodents have very high amounts of circulating leptin, this hyperleptinemia is associated with leptin resistance which neither reduces appetite nor increases energy expenditure\cite{39}

Apelin has been reported as a beneficial adipokine up-regulated in obesity as an attempt to overcome either insulin resistance or obesity-related cardiovascular diseases\cite{40}, elevated plasma apelin has been estemated in moderately\cite{41} and in severe obese\cite{42}. It has also been shown that plasma apelin levels were increased in diabetic subjects and positively correlated with BMI, HOMA-IR and fasting plasma insulin\cite{43}, suggesting a role of apelin in the pathogenesis of type II diabetes induces by overweight\cite{44},

Watanabe et al.\cite{45} stated that disturbed ECs levels that accompanied HFD are related to onset, duration and its fatty acid composition.

Cannabinoids promote lipogenesis and the storage of adipose tissue via CB\textsubscript{1}, and the expression of CB\textsubscript{1} in adipose tissue is up-regulated in rodent models of obesity\cite{15,46},

On the other hand, antagonists of CB\textsubscript{1} promote lipolysis and fatty acid oxidation and increase in insulin sensitivity\cite{47,48}.

As regard the comparison between the HFrD and the normal diet fed groups, HFrD fed group showed a significant increase in final body weight with preservation of its correlation with all metabolic parameters and a significant increase in fasting serum glucose levels, fasting serum insulin levels, and HOMA-IR, HFrD fed group also showed dyslipidemia proved by significant increase serum total cholesterol, serum triglyceride, VLDL-cholesterol levels, and LDL-cholesterol, accompanied by a significant decrease in HDL-cholesterol.

These data are in line with studies on rodents that stated that HFrD increases intra hepatocellular lipid and stimulates hepatic de novo lipogenesis within a few days and induce hyperlactatemia and hypertriglyceridemia\cite{49}. Studies of pure fructose fed to laboratory animals show increased plasma free fatty acids, and abdominal adipose tissue, as well as impaired insulin sensitivity\cite{50}.

Fructose consumption by adult rats has been shown to produce diminished glucose tolerance and insulin sensitivity as well as elevated TG, cholesterol, and body fat\cite{51}. The insulin resistance in this animal model probably results from the impairment of insulin-stimulated glucose uptake in insulin-responsive tissues as well as changes in hepatic glucose metabolism\cite{52}. Insulin resistance may also contributed to this hypertriglyceridemia by reducing the inhibitory effect of insulin on TG secretion rate in the liver of fructose fed rats\cite{53}.

The increase in TG level may be due to stimulation of hepatic VLDL-triacylglycerol synthesis and secretion and decreased VLDL-triacylglycerol clearance\cite{54}. Stanhope et al.\cite{55} indicate an increase in weight gain on diets rich in fructose, and a correlation between body fat and circulating TG has been established. In addition, HFrD induce leptin and insulin resistance. Taken together, leptin or insulin resistance and elevated TG serum levels may cause food over-consumption and contribute to the corresponding obesity, moreover, ingesting fructose-sweetened food raises calorie intake resulting in an over-consumption of energy which is not balanced by energy output, leading to weight gain\cite{55}.

As regard the comparison between HFD and HFrD fed groups, both groups showed dyslipidemia and glucose intolerance, however there were no significant differences between both groups in final body weight, fasting serum levels of glucose, insulin, total cholesterol, HDL-cholesterol, and LDL-cholesterol and HOMA-IR. While a significant increase in serum triglyceride, VLDL-cholesterol in HFrD fed group when compared with HFD fed group. These data are in consistent with that of Liu and Manson\cite{57} who proved that diet high in carbohydrates is associated with glucose intolerance and obesity.

One of the main differences between glucose and fructose metabolism is that glucose must advance through a negatively regulated step using phosphofructokinase which regulates glycolysis in the liver. Fructose can bypasses this regulatory step and continue to be metabolized in the liver into glycerol-3-phosphate and acetyl coenzyme, these latter metabolites serve as substrates for glyceride synthesis leading to increased formation of VLDL and TG in the liver\cite{58}. In contrast to glucose, when large amounts of fructose are ingested, the glycolytic pathway becomes saturated, and TG production is facilitated\cite{59}.

The present results showed an insignificant disturbance in all metabolic parameters measured in methanandamide treated normal diet pair fed group and methanandamide treated HFD pair fed group and methanandamide treated HFrD pair fed group when
compared with that of normal diet fed, HFD fed, and HFrD fed control groups respectively. However, methanandamide treated normal diet ad libitum showed a significant disregulation of glucose metabolism 

et al. who suggested that the effect of ECS on disturbing the metabolism is due to increase food intake, depending in their study on the anorectic effect of the CB1 blocker (AM 251) they observed that subchronic AM251 treatment in ob/ob mice caused weight reduction, improved the impaired metabolism and decrease insulin resistance, but these observations were found also in pair-fed control animals suggesting that the beneficial actions of CB1 receptor antagonism is due to reduced food intake.

Specific central CB1 blockade decreased body weight and food intake in diet induced obese rats, but had no beneficial effects on glucose metabolism; on the other hand, peripheral CB1 blockade also reduced food intake and body weight but, in addition, enhanced insulin sensitivity. However, this improvement in insulin sensitivity was also detected in vehicle pair-fed rats, which suggest that decreased energy intake was the major factor responsible for these effects.

Finally, collecting data from previous researches concerning with ECS and ECs benefits revealed that ECS have been used therapeutically for alleviating pain, and induces neuroprotection in ischemic brain areas. Moreover, endocannabinoid signaling was proposed to protect against the consequences of stress in a certain dose range as low doses of methanandamide was proved to induce anxiolytic effects which are CB1 receptor-mediated. In addition, CB1 receptor activation at amygdala promotes fear extinction. Cannabinoids are also effective in treatment of models of nausea and vomiting, gastric ulcers, irritable bowel syndrome, ulcerative colitis, Crohn’s disease, secretory diarrhea, paralytic ileus and gastro-esophageal reflux disease.

In fact, many side effects related to the use of CB1 receptor antagonists were proved as impairs fear extinction, increases anxiety-related behaviour in the elevated plus maze. In addition, both pharmacological antagonism and genetic inactivation of CB1 receptors impair extinction of conditioned fear memories. Moreover, acute injections of rimonabant or AM251 (CB1 antagonists) also increase both basal and stress-induced serum corticosterone levels. Furthermore, mice lacking CB1 receptors are impaired in actively coping with stress in a model predictive for antidepressant-like activity. Thus, CB1 receptor antagonism may induce psychiatric side-effects, in humans, mainly anxiety- and depression-like states, being in accordance with the notion that the endocannabinoid system acts to keep a set point counteracting aversive emotions. Obese patients already suffer from anxiety or depression more frequently than non-obese subjects.

Taken together with the results of the present study, it can be concluded that ECS should not be palmed for metabolic disturbances but the type and amount of diet is the main cause and its receptors antagonists must not be the main target for treatment obesity.

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