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Original Roles of G1359A polymorphism of the cannabinoid receptor gene (CNR1) on weight loss and adipocytokines after a hypocaloric diet

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Abstract

Background: A intragenic biallelic polymorphism (1359 G/A) of the CB1 gene resulting in the substitution of the G to A at nucleotide position 1359 in codon 435 (Thr), was reported as a common polymorphism in Caucasian populations. Intervention studies with this polymorphism have not been realized.

Objective: We decided to investigate the role of the polymorphism (G1359A) of CB1 receptor gene on adipocytokines response and weight loss secondary to a lifestyle modification (Mediterranean hypocaloric diet and exercise) in obese patients.

Design: A population of 94 patients with obesity was analyzed. Before and after 3 months on a hypocaloric diet, an anthropometric evaluation, an assessment of nutritional intake and a biochemical analysis were performed. The statistical analysis was performed for the combined G1359A and A1359A as a group and wild type G1359G as second group, with a dominant model.

Results: Forty seven patients (50%) had the genotype G1359G (wild type group) and 47 (50%) patients G1359A (41 patients, 43.6%) or A1359A (6 patients, 6.4%) (mutant type group) had the genotype. In wild and mutant type groups, weight, body mass index, fat mass, waist circumference and systolic blood pressure decreased. In mutant type group, resistin (4.15 ± 1.7 ng/ml vs. 3.90 ± 2.1 ng/ml: P < 0.05), leptin (78.4 ± 69 ng/ml vs 66.2 ± 32 ng/ml: P < 0.05) and IL-6 (1.40 ± 1.9 pg/ml vs 0.81 ± 1.5 pg/ml: P < 0.05) levels decreased after dietary treatment.

Conclusion: The novel finding of this study is the association of the mutant allele (A1359) with a decrease of resistin, leptin and interleukin-6 secondary to weight loss.

PAPEL DEL POLIMORFISMO G1359A DEL GEN DEL RECEPTOR ENDOCANABINOIDE TIPO I (CNR1) EN LA PERDIDA DE PESO Y ADIPOCITOQUINAS TRAS UNA DIETA HIPOCALÓRICA

Resumen

Antecedentes: Un polimorfismo intragénico (1359 G / A) del gen del receptor CB1 que produce la sustitución en la posición 1359 en el codón 435 (Thr), se ha descrito como un polimorfismo común en poblaciones caucásicas. No se han realizado estudios de intervención dietética teniendo en cuenta este polimorfismo.

Objetivo: Se decidió investigar el papel del polimorfismo (G1359A) del gen del receptor CB1 en el estilo de vida (dieta mediterránea hipocalórica y ejercicio) en pacientes obesos.

Diseño: Se analizó una población de 94 pacientes con obesidad. Antes y tras 3 meses con una dieta hipocalórica se realizaron una evaluación antropométrica, una evaluación de la ingesta nutricional y un análisis bioquímico. El análisis estadístico se realizó combinando G1359A y A1359A como grupo mutado y G1359G como genotipo (modelo dominante).

Resultados: Cuarenta y siete pacientes (50%) tenían el genotipo G1359G (grupo genotipo salvaje) y 47 (50%) pacientes G1359A (41 pacientes, 43.6%) o A1359A (6 pacientes, 6.4%) (grupo genotipo mutante) tenían el genotipo. En el grupo genotipo salvaje, la resistina (4,15 ± 1,7 ng/ml vs. 3,90 ± 2,1 ng/ml: P < 0.05), leptina (78,4 ± 69 ng/ml vs 66,2 ± 32 ng/ml: P < 0.05) y la IL-6 (1,40 ± 1,9 pg/ml vs 0,81 ± 1,5 pg/ml: P < 0.05) disminuyeron después del tratamiento dietético.

Conclusión: El resultado más importante es la asociación del alelo mutado con una disminución de los niveles de resistina, leptina e interleukina-6 tras la perdida de peso con la dieta.

Key words: Adipocytokines. Cannabinoid receptor gene. Hypocaloric diet. Obesity.

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Introduction

Weight reduction is known to be an effective treatment for overweight-obese patients with risk factors of metabolic syndrome and adipocytokines. The current view of adipose tissue is that of an active secretor organ, sending out and responding to signals that modulate appetite, insulin sensitivity, energy expenditure, inflammation and immunity.

In this scenario, the important role played by endocannabinoid system is emerging: it controls food intake, energy balance and lipid and glucose metabolism through both central and peripheral effects, and stimulated lipogenesis and fat accumulation. Herbal Cannabis sativa (marijuana) has been known to have many psychoactive effects in humans including increases in body weight. Nevertheless, the mechanism underlying cannabinoide neurobiological effects have been recently revealed. The endogenous cannabinoid system mediates and it’s positioned both functionally and anatomically to be an important modulator of normal human brain behavior. This system consists of endogenous ligands 2-arachidonoylglycerol (2-AG) and anandamide (ADA) and two types of G-protein-coupled cannabinoid receptors: Cannabinoid type-1 receptor (CB1), located in several brain areas and in a variety of peripheral tissues including adipose tissue, and CB2, present in the immune system. A greater insight into the endocannabinoid system has been derived from studies in animals with a genetic deletion of the CB1 receptor, which have a lean phenotype and are resistant to diet-induced obesity and the associated insulin resistance induced by a high palatable high-fat diet. A silent intragenic biallelic polymorphism (1359 G/A) of the CB1 gene resulting in the substitution of the G to A at nucleotide position 1359 in codon 435 (Thr), was reported as a common polymorphism (1359 G/A) of the CB1 gene resulting in the substitution of the G to A at nucleotide position 1359 in codon 435 (Thr), was reported as a common polymorphism in the German population, reaching frequencies of 24-32% for the allele (A).

Considering the evidence that endogenous cannabinoid system plays a role in metabolic aspects of body weight and feeding behavior and that long-term maintenance of body weight is determined by balance between energy intake and expenditure. We decide to investigate the role of the polymorphism (G1359A) of CB1 receptor gene on adipocytokines response and weight loss secondary to a lifestyle modification (Mediterranean hypocaloric diet and exercise) in obese patients.

Subjects and methods

Subjects

A population of 94 obesity (body mass index > 30) non-diabetic outpatients was analyzed in a prospective way. These patients were recruited in a Nutrition Clinic Unit. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving patients were approved by the HURH ethics committee. Written informed consent was obtained from all patients. Exclusion criteria included history of cardiovascular disease or stroke during the previous 36 months, total cholesterol > 300 mg/dl, triglycerides > 400 mg/dl, blood pressure > 140/90 mmHg, fasting plasma glucose > 110 mg/dl, as well as the use of sulphonylurea, thiazolidinedions, insulin, glucocorticoids, antineoplastic agents, angiotensin receptor blockers, angiotensin converting enzyme inhibitors and psychoactive medications. Local ethical committee approved the protocol.

Procedure

The lifestyle modification program was a hypocaloric diet (1,520 kcal, 52% of carbohydrates, 25% of lipids and 23% of proteins) and exercise. The exercise program consisted of aerobic exercise for at least 3 times per week (60 minutes each).

Weight, blood pressure, fasting glucose, c-reactive protein (CRP), insulin, insulin resistance (HOMA), total cholesterol, LDL-cholesterol, HDL-cholesterol, plasma triacylglycerol concentration and adipocytokines (leptin, adiponectin, resistin, TNF alpha, and interleukin 6) levels were measured at basal time. A tetrapolar bioimpedance, an indirect calorimetry and a prospective serial assessment of nutritional intake with 3 days written food records were realized. Genotype of CB1 receptor gene polymorphism was studied.

Genotyping of CB1 gene polymorphism

Oligonucleotide primers and probes were designed with the Beacon Designer 4.0 (Premier Biosoft International®, LA, CA). The polymerase chain reaction (PCR) was carried out with 50 ng of genomic DNA, 0.5 uL of each oligonucleotide primer (primer forward: 5’-TTTC ACA GGG CCG CAG AAA G-3’ and reverse 5’-GAG GCA TCA GGC TCA CAG AG-3’), and 0.25 uL of each probes (wild probe: 5’-Fam-ATC AAG AGC ACA TCA GGC TCA CAG AG-3’, and mutant probe: 5’-Texas red- ATC AAG AGC ACA GTC AAG ATT GCC -BHQ-1-3’) in a 25 uL final volume (Termociclador iCycler IQ (Bio-Rad®), Hercules, CA). DNA was denaturated at 95°C for 3 min; this was followed by 50 cycles of denaturation at 95°C for 15 s, and annealing at 59.3°C for 45 s. The PCR were run in a 25 uL final volume containing 12.5 uL of IQTM Supermix (Bio-Rad®, Hercules, CA) with hot start Taq DNA polymerase. Hardy Weinberger equilibrium was assessed.

Assays

Plasma glucose levels were determined by using an automated glucose oxidase method (Glucose analyser

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Insulin was measured by RIA (RIA Diagnostic Corporation, Los Angeles, CA) with a sensitivity of 0.5 mU/L (normal range 0.5–30 mU/L) and the homeostasis model assessment for insulin sensitivity (HOMA) was calculated using these values.

CRP was measured by immunoturbimetry (Roche Diagnostics GmbH, Mannheim, Germany), with a normal range of (0–7 mg/dl) and analytical sensitivity 0.5 mg/dl. Lipoprotein (a) was determined by immunonephelometry with the aid of a Beckman array analyzer (Beckman Instruments, Calif., USA).

Serum total cholesterol and triglyceride concentrations were determined by enzymatic colorimetric assay (Technicon Instruments, Ltd., New York, N.Y., USA), while HDL cholesterol was determined enzymatically in the supernatant after precipitation of other lipoproteins with dextran sulfate-magnesium. LDL cholesterol was calculated using Friedewald formula.

Adipocytokines

Resistin was measured by ELISA (Biovendor Laboratory, Inc., Brno, Czech Republic) with a sensitivity of 0.2 ng/ml with a normal range of 4–12 ng/ml. Leptin was measured by ELISA (Diagnostic Systems Laboratories, Inc., Texas, USA) with a sensitivity of 0.05 ng/ml and a normal range of 10–100 ng/ml. Adiponectin was measured by ELISA (R&D systems, Inc., Mineapolis, USA) with a sensitivity of 0.246 ng/ml and a normal range of 8.65–21.43 ng/ml. Interleukin 6 and TNF alpha were measured by ELISA (R&D systems, Inc., Mineapolis, USA) with a sensitivity of 0.7 pg/ml and 0.5 pg/ml, respectively. Normal values of IL6 was (1.12–12.5 pg/ml) and TNF-alpha (0.5–15.6 pg/ml).

Indirect calorimetry

For the measurement of resting energy expenditure, subjects were admitted to a metabolic ward. After a 12 h overnight fast, resting metabolic rate was measured in the sitting awake subject in a temperature-controlled room over one 20 min period with an open-circuit indirect calorimetry system (standardized for temperature, pressure and moisture) fitted with a face mask (MedGem;Health Tech, Golden, USA), coefficient of variation 5%. Resting metabolic rate (kcal/day) and oxygen consumption (ml/min) were calculated.

Anthropometric measurements

Body weight was measured to an accuracy of 0.5 kg and body mass index computed as body weight/(height$^2$). Waist (narrowest diameter between xiphoid process and iliac crest) and hip (widest diameter over greater trochanters) circumferences to derive waist-to-hip ratio (WHR) were measured, too. Tetrapolar body electrical bioimpedance was used to determine body composition with an accuracy of 0.5 g. An electric current of 0.8 mA and 50 kHz was produced by a calibrated signal generator (Biodynamics Model 310e, Seattle, WA, USA) and applied to the skin using adhesive electrodes placed on right-side limbs. Resistance and reactance were used to calculate total body water, fat and fat-free mass.

Blood pressure was measured twice after a 10 minutes rest with a random zero mercury sphygmomanometer, and averaged.

Dietary intake and habits

Patients received prospective serial assessment of nutritional intake with 3 days written food records. All enrolled subjects received instruction to record their daily dietary intake for three days including a weekend day. Handling of the dietary data was by means of a personal computer equipped with personal software, incorporating use of food scales and models to enhance portion size accuracy. Records were reviewed by a diettian and analysed with a computer-based data evaluation system. National composition food tables were used as reference. Regular aerobic physical activity (walking was allowed, no other exercises) was maintained during the period study for at least 3 times per week (60 minutes each).

Statistical analysis

Sample size was calculated to detect differences over 2 kg in body weight with 90% power and 5% significance (n = 90, 45 in each group). The results were expressed as average ± standard deviation. The distribution of variables was analyzed with Kolmogorov-Smirnov test. Quantitative variables with normal distribution were analyzed with a two-tailed Student’s-t test. Non-parametric variables were analyzed with the U-Mann-Whitney test. Qualitative variables were analyzed with the chi-square test, with Yates correction as necessary, and Fisher’s test. The statistical analysis was performed for the combined G1359A and A1359A as a group and wild type G1359G as second group, with a dominant model. A p-value < 0.05 was considered significantly.

Results

Ninety four patients gave informed consent and were enrolled in the study. The mean age was 45.2 ± 17 years and the mean BMI 34.4 ± 5.1, with 24 males (25.5%) and 70 females (74.5%).

All subjects were weight stable during the 2 weeks period preceding the study (body weight change, 0.23
± 0.1 kg). Forty seven patients (50%) had the genotype
G1359G (wild type group) and 47 (50%) patients
G1359A or A1359A (41 patients, 43.6%) or
A1359A (6 patients, 6.4%) (mutant type group) had the genotype. Age was
similar in both groups (wild type: 42.95 ± 16.6 years
vs mutant group: 45.1 ± 16.8 years: ns). Sex distribution
was similar in both groups, males (23.4% vs
27.7%) and females (76.6% vs 72.3%).

Table I shows the differences in anthropometric
variables. No differences were detected among basal
and post-treatment values of anthropometric variables
between both genotypes. In wild and mutant type
groups, weight, body mass index, fat mass, waist cir-
cumference and systolic blood pressure decreased.

Table II shows the classic cardiovascular risk fac-
tors. No differences were detected among basal and
post-treatment values of biochemical variables
between both genotypes. The improvement in all vari-
ables was not statistically significant.

Table III shows nutritional intake with 3 days writ-
ten food records. No statistical differences were
detected in calorie, carbohydrate, fat, and protein
intakes. Aerobic exercise per week was similar in both
groups, with a significant increase during the protocol.

Table IV shows levels of adipocytokines. No differ-
ences were detected among basal values of cytokines
variables between both genotypes. In mutant type
group, resistin, leptin and IL-6 levels decreased after
dietary treatment.

Discussion

The finding of this study is the association of the
G1359A and A1359A CB1 genotypes with a signifi-
cant decrease on leptin, resistin and IL-6 levels after
weight loss.

We do not know how the A1359 allele may exert an
influence on adipocytokines levels before weight loss.

However, the literature supports the notion that endo-
cannabinoid system is positioned for regulation of
endocannabinoid levels that could influence craving

Table I
Changes in anthropometric variables

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>G1359G 0 time</th>
<th>G1359G At 3 months</th>
<th>G1359A or A1359A 0 time</th>
<th>G1359A or A1359A At 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>33.9 ± 5.3</td>
<td>33.1 ± 5.3</td>
<td>34.5 ± 4.5</td>
<td>33.2 ± 4.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>89.2 ± 18.5</td>
<td>86.9 ± 17.7</td>
<td>87.8 ± 14.7</td>
<td>84.5 ± 14.6</td>
</tr>
<tr>
<td>Fat free mass (kg)</td>
<td>48.3 ± 14.1</td>
<td>49.2 ± 11.5</td>
<td>47.8 ± 12.6</td>
<td>46.7 ± 10.7</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>38.1 ± 13.2</td>
<td>35.7 ± 12.8</td>
<td>38.9 ± 12.7</td>
<td>36.9 ± 12.4</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>107.3 ± 15.5</td>
<td>104.9 ± 15.4</td>
<td>107.3 ± 19</td>
<td>102.9 ± 19.8</td>
</tr>
<tr>
<td>Waist to hip ratio</td>
<td>0.9 ± 0.1</td>
<td>0.91 ± 0.09</td>
<td>0.92 ± 0.1</td>
<td>0.91 ± 0.09</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>134 ± 18.1</td>
<td>122.3 ± 11.6</td>
<td>130 ± 12.1</td>
<td>126 ± 12.5</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>80.8 ± 8.9</td>
<td>83.6 ± 9.3</td>
<td>77.9 ± 8.2</td>
<td>77.4 ± 2.8</td>
</tr>
<tr>
<td>RMR (kcal/day)</td>
<td>1,733 ± 419</td>
<td>1,837 ± 543</td>
<td>1,784.5 ± 479</td>
<td>1,859 ± 436</td>
</tr>
</tbody>
</table>

RMR: resting metabolic rate.

* p < 0.05, in each group with basal values.

Table II
Classical cardiovascular risk factors

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>G1359G 0 time</th>
<th>G1359G At 3 months</th>
<th>G1359A or A1359A 0 time</th>
<th>G1359A or A1359A At 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dl)</td>
<td>99.5 ± 18.4</td>
<td>97.1 ± 14.3</td>
<td>98.4 ± 17.7</td>
<td>95.7 ± 13.9</td>
</tr>
<tr>
<td>Total ch. (mg/dl)</td>
<td>203.9 ± 40</td>
<td>198.7 ± 31</td>
<td>202.2 ± 49</td>
<td>204.8 ± 40.4</td>
</tr>
<tr>
<td>LDL-ch. (mg/dl)</td>
<td>121.4 ± 41</td>
<td>103.4 ± 47</td>
<td>138.9 ± 53</td>
<td>123.1 ± 44.6</td>
</tr>
<tr>
<td>HDL-ch. (mg/dl)</td>
<td>54.0 ± 14.1</td>
<td>53.1 ± 15.6</td>
<td>56.8 ± 12</td>
<td>57.1 ± 20</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>122.7 ± 57</td>
<td>122.4 ± 59.5</td>
<td>115.3 ± 49</td>
<td>114.2 ± 83</td>
</tr>
<tr>
<td>Lp (a) (mg/dl)</td>
<td>26.7 ± 39</td>
<td>26.2 ± 25</td>
<td>27.6 ± 40</td>
<td>35.2 ± 23</td>
</tr>
<tr>
<td>Insulin (mUI/L)</td>
<td>13.3 ± 7.3</td>
<td>12.5 ± 9.3</td>
<td>13.4 ± 6.7</td>
<td>13.8 ± 8.4</td>
</tr>
<tr>
<td>HOMA</td>
<td>3.37 ± 2.5</td>
<td>3.15 ± 2.6</td>
<td>3.4 ± 1.8</td>
<td>3.4 ± 2.2</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>6.2 ± 7.8</td>
<td>5.3 ± 7.6</td>
<td>6.1 ± 7.6</td>
<td>5.3 ± 5.1</td>
</tr>
</tbody>
</table>

and reward behaviors through the relevant neuronal circuitry and metabolic parameters. This provides a link between the consequences of this polymorphism and the present study indicating that the CB1 receptor G1359A polymorphism may be one risk factor for susceptibility to obesity and metabolic abnormalities. Also, the CB1 receptor is expressed in some peripheral human tissue studied in relation to the pathogenesis of obesity and obesity-associated metabolic disorders and marked down-regulation of the fatty acid amide hydrolase (FAAH) gene expression was found in the adipose tissue, suggesting that adipose tissue may be an important contributor to endocannabinoid metabolism, with unknown relations between this system and adipocytokines.

In our study the prevalence of GA genotype was (41%), similar that other studies; 43.5%, 19.6% and 33.1%. However, a lack of association between body mass index and this polymorphism is present in our results; this fact is in contrast with the association detected by Gazerro et al. with SNP G1359A of CB1 receptor, A3813A and A4895A SNPs of CB1 receptor and with (G1422A) SNP of CB1 receptor. Benzino et al. shows a positive correlation of the A10908G and T5489C polymorphisms with obesity in two obese populations. The inconsistencies between association studies may reflect the complex interactions between multiple population-specific genetic and environmental factors. Perhaps, these different results could be explained by bias secondary to an unmeasured dietary intake. These previous studies would require composition analysis of the diet to determine whether dietary components could be responsible for the lipid profile modifications. In our study dietary intake did not show basal statistical differences between groups, and a hypocaloric diet has been used as an intervention therapy.

Ravinet et al. found that CB-1 gene-deficient mice were lean and resistant to diet-induced obesity and showed reduced plasma insulin and leptin levels. In our patients, leptin, resistin and IL-6 levels decreased secondary to weight loss in obese patients carrying the mutant type CB1 allele (G/A and A/A). This metabolic relationship between the polymorphism and cardiovascular risk factors has been detected by the next study. Alberle et al. have shown that carriers of at least one A allele in CB1 lost more weight and reduced LDL cholesterol than wild type patients. However this study did not measure adipocytokines to explore this data.

The theoreical explanation of this relationship with adipocytokines could be due by the own adipose tissue metabolism. Cannabinoids modulate the expression of several cellular target genes via the CB1 receptor dependent pathway. In brown adipose tissue, cannabinoid antagonist treatment is able to stimulate the expression of genes favoring energy dissipation through mitochondrial heat production. Other evidence of this interaction (metabolism of adipose tissue and endocannabinoid system is the increase expression of adiponectin induced by CB1 antagonists, in vitro, in

<table>
<thead>
<tr>
<th>Table III</th>
<th>Dietary intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>G1359G</td>
</tr>
<tr>
<td></td>
<td>0 time</td>
</tr>
<tr>
<td>Energy (kcal/day)</td>
<td>1,650 ± 478</td>
</tr>
<tr>
<td>CH (g/day)</td>
<td>163.8 ± 60</td>
</tr>
<tr>
<td>Fat (g/day)</td>
<td>73.4 ± 21.3</td>
</tr>
<tr>
<td>Protein (g/day)</td>
<td>82.8 ± 25</td>
</tr>
<tr>
<td>Exercise (hs./week)</td>
<td>1.0 ± 2.1</td>
</tr>
</tbody>
</table>

*p < 0.05, in each group with basal values. CH: Carbohydrate.

<table>
<thead>
<tr>
<th>Table IV</th>
<th>Circulating adipocytokines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>G1359G</td>
</tr>
<tr>
<td></td>
<td>0 time</td>
</tr>
<tr>
<td>IL6 (pg/ml)</td>
<td>0.96 ± 1.4</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>6.92 ± 3.4</td>
</tr>
<tr>
<td>Adiponectin (ng/ml)</td>
<td>27.9 ± 28.1</td>
</tr>
<tr>
<td>Resistin (ng/ml)</td>
<td>4.20 ± 1.5</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>80.6 ± 73</td>
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</table>

*p < 0.05, in each group with basal values.
3T3 F442A adipocytes and in vivo obese mice. \(^1\) suggests a close relationship between CB1 receptor blockade and the production of this adipocyte-derived protein. Rimonabant (a selective CB1-receptor blockade) has demonstrated an increase in adiponectin levels in the RIO-Lipids study.\(^2\)

Other possible links have been investigated in animal models. Thanos et al.\(^3\) have demonstrated that leptin receptor deficiency is associated with upregulation of cannabinoid 1 receptors in limbic brain regions. In other animal models,\(^4\) a novel hormonal crosstalk between leptin and glucocorticoids that rapidly modulates synaptic excitation via endocannabinoid release in hypothalamus and provides a nutritional state-sensitive mechanism has been described.

In conclusion, the novel finding of this study is the association of the mutant allele (A1359) with a decrease of resistin, leptin and interleukin-6 secondary to weight loss. Further studies are needed to elucidate this complex relationship and the theoretical therapeutically implications.

References